Volume 32, Number 3, December, 1959

The Yale Journal of Biology & Medicine

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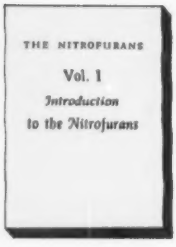

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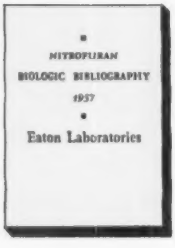

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Entered as second-class matter January 11, 1929, at the post office at New Haven, Connecticut, under the Act of March 3, 1879.

PRINTED BY THE VAN DYCK PRINTING CO., NEW HAVEN, CONN.

MILTON CHARLES WINTERNITZ IN 1957

MILTON CHARLES WINTERNITZ

February 19, 1885—October 3, 1959

Time, like an ever-rolling stream,
Bears all its sons away:
They fly forgotten, as a dream
Dies at the opening day.

These lines of Isaac Watts apply to most men, but not to Milton Charles Winternitz. For us who came to know him, "Winter" remains a vital, vivid presence. Who could forget this compact, intense fountainhead of energy; this inexhaustible generator of ideas and constant stimulator of the imagination; this goad and second conscience; this sensitive, perceptive, and, in his own way, tender human being who inspired adulation? Winter would not condone any dwelling on the past, but when we look back on him and his works, we find ourselves not in the past but in the future, since what he conceived has yet to come to full fruition. It is in this spirit that we presume to write.

EARLY DAYS

It was no doubt stimulating to be reared as he was in the bosom of an intelligent immigrant medical family responding to the challenge of the new world in the bustling Baltimore of the eighties and nineties. Selling "penny insurance" to the humbler families of his native city gave Winter money for his education at Johns Hopkins and undoubtedly was the beginning of his keen knowledge of people, a conspicuous ingredient of his later success. An occasional mingling with "the more elegant of Eutaw Place" was also to stand him in good stead. When he reached medical school, Winter was enraptured by the spirit and opportunities of the then young Hopkins. William Henry Welch had borne the light of German laboratory medicine to America and had assembled the first great medical faculty of that school. Their example and their students, many of whom went on to chairs elsewhere, exerted a profound influence on the attitudes and on the teaching of medicine in this country. Winter's horizons were already wide, and in the summer of 1904 we find the young medical student on a visit to Chicago observing Lillie's effort to make medicine a part of the School of Biological Sciences and to bring the medical faculty into "full time." This too may have exerted an influence on his future thinking.

Continuing his studies at the Hopkins, he found the laboratories full of men with ideas, joyfully at work. What greater stimulus could a youngster have than to explore things for himself under the guidance of these pre-

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ceptors? His first paper, published in German while he was still in his second year in medicine, dealt with the enzyme adenase. His interest in enzymes persisted, and in this he anticipated a whole school of pathologists currently preoccupied with the histochemistry of these substances.

Miss Effie Taylor, a nursing student of those days at the Johns Hopkins Hospital and later Dean of the Yale School of Nursing, recalls his indefatigability on the wards and his sympathetic and winsome manner with the patients. His brilliance as a student attracted attention, but he failed by a single place to receive a coveted appointment to Halsted's House Staff in surgery. Rather, perhaps fortunately for the recent history of medicine and of Yale, he fell under the direct influence of the great Welch and into the stimulating company of such younger men as Whipple and MacCallum. Welch's extensive travels, wide interests, and multifarious preoccupations precipitated frequent, unannounced absences, and called for the instant availability of his juniors. These, including Winter, had always to be prepared to present a lecture or conduct a class scheduled in the name of The Chief. It was excellent experience for young teachers to aim so high, and no complaints from their students have descended to posterity. Winter's capacity for extemporaneous eloquence and for making himself unmistakably clear was no doubt partly developed in the lecture halls of the early Hopkins. During this period he made several short visits to Europe, the first in 1907, simply to "look around." In 1910 he again visited Leipzig, Berlin, Freiburg, Vienna, and tarried for a time at Marchand's laboratory, but not for concentrated work in a single subject. Rather, he simply observed methods, watched and learned a great deal from autopsies as no one but a keen observer can, and thought a great deal.

Welch's satisfaction in this dashing, tireless pupil, by then an Associate Professor, was reflected in his suggesting him for the Chair of Pathology at Yale. The year was 1917, and Winter himself was reluctant since he wished to go to war with the Hopkins Medical Unit. It may well be that Welch, an alumnus of Yale College, glimpsed in Winter the means of breathing new life into the medical school of his honored alma mater. Welch prevailed, and in this way, in the words of John Fulton, "the Hopkins discharged the very considerable debt it owed to Yale."

FIRST OPPORTUNITIES IN NEW HAVEN

In 1917, Dr. Winternitz found himself occupying a rather unpadded Chair, but with opportunities unlimited. How often throughout his life thereafter he used that word, "opportunity," to stir men to become their best selves; and who used opportunity better than himself? Little did Welch

know what a grand settee this chair was soon to become! This firebrand of 32 years—"Napoleonic in outlook and stature," undecorous, unfettered by tradition, deviant in background—was at first held somewhat at arm's length by the University authorities. But this only made the challenge greater.

The first World War was raging, gas warfare had begun, and he at once saw the need for biological study of these new agents. His appearance before an Advisory Committee of the Secretary of War is described by Dr. Arthur Ruggles, a member, in these words: ". . . of all the great scientists who appeared before it, he was the only one who had the courage to state things as he saw them, had the remedies always at hand, and at times almost ruthlessly, but necessarily, brushed aside opposition, compromise and mediocrity." He then obtained the permission of the University to establish a center for the study of the biological effects of war gases, and also an Army training school for laboratory medicine. The latter occupied a large temporary building, the "Barrack" on the site of what is now the east wing of Brady Laboratory and Lauder Hall. The former was housed in a large square sandstone building later to become well known to generations of medical students as Nathan Smith Hall, a nursing dormitory. In addition, as part of his new duties, Major Winternitz supervised a similar laboratory in Washington. His schedule in those days before the airplane involved trips to Washington every Sunday, to a gas plant in Lakewood, New Jersey, on Tuesday, with return to New Haven for Thursday, Friday and Saturday to direct the two major army laboratories in New Haven, and to carry his load, as he did incomparably well, of teaching. This work for the army offered the first great exercise of his genius for organization. He was able to effect a successful alloyage of military and civilian minds, always a difficult task, and more so in those days of less experience. His uncanny ability to select the right people for certain jobs is exemplified even then in his associates on the gas warfare problem, among whom were R. A. Lambert, later of the Rockefeller Institute; George B. Wislocki, later Professor of Anatomy at Harvard; and George Hathorn Smith, the well-loved Professor of Bacteriology and Immunology in this institution and founder of *The Yale Journal of Biology and Medicine*. Leon Stone, now Bronson Professor of Comparative Anatomy at Yale, was employed as a technician and Armin Hemberger as artist.

The monograph, *The Pathology of War Gas Poisoning* was published by the Yale Press in 1920 under his editorship, and a companion volume *The Pathology of Influenza* was produced in the same year. In the latter, the best was made of an unprecedented opportunity to perform a definitive investigation of a previously little-known disease. Both monographs have

become classics for their organization, detail of observation, and clarity and skill of illustration, and have remained important works of reference.

DEAN WINTERNITZ

Dr. Winternitz' greatest opportunity, and that of the Yale School of Medicine, came in 1920 when he was appointed to the deanship. This reflected a growing confidence on the part of Woodbridge Hall. At that time the fortunes of the school were at their lowest. Speculation had been rife that it would be abandoned altogether. It was pictured as a small boat tossed on angry sea, about to be abandoned by the coxswain, with two members of the crew paddling in opposite directions, and hardly worthy to be the target of the many torpedoes aimed at it; further, the launchers of these missiles were shown as hostile to each other. In that remarkable document *The Past, Present and Future of the Yale School of Medicine* there are recorded, as a sort of Magna Charta, the principles adopted by the Yale Corporation in 1920:

1. That there is a clear and definite opportunity and obligation of the University to Medical Education.
2. That the Yale School of Medicine has a valuable nucleus of men and material and sound traditions, which richly justify the development of an institution for medical education of the highest type.
3. That the Corporation accept as a policy the development of a Medical School of the highest type to include the pre-clinical and clinical years of instruction upon such principles of medical education as may be approved by the Corporation, after conference with the Medical Faculty.
4. That every effort be made to obtain at the earliest possible date the necessary funds with which to expand and develop the buildings, the equipment, the instruction and the research, and the service, in accordance with the best ideals of modern medical education—as an essential unit of our University Plan of Development.

Now came the time to implement this good intent. The closer affiliation between the Medical School and the New Haven Hospital had already been brought about by an agreement made in 1912 and this was consolidated by the construction of the first wing of the laboratory on the Anthony N. Brady Foundation. In 1920, the Prudential Committee of the Yale Corporation made the decision "To request the Sterling Trustees to set aside $1,320,000 toward a Medical School Building"; the Sterling Hall of Medicine was completed in 1923. Winter's magical talents in transmitting his visions with color and intensity to men of means were now at their fullest. His reports as Dean from 1920 to 1935 are a stirring record of the elevation of this School from near desuetude to eminence; more than this, they recount the development of ideas which are its priceless intellectual heritage.

The dynamic new Dean attracted strong support from the General Education Board (Anson Phelps Stokes of Yale was a member), from the Rockefeller Foundation, and from generous persons interested in Yale. The "Barrack" was replaced by an expansion of the Brady Laboratory and by Farnam and Lauder Halls. Modern wards rose to substitute for outmoded pavillions, and the Laboratory for Medicine and Pediatrics was created, largely on the basis of a $2,000,000 grant from the General Education Board. The foundations for the now splendid Medical Library were laid. At the end of the first ten years, Dean Winternitz was able to report that $5,780,000 had been put into the New Haven Hospital, and $5,650,000 into other developments in the School of Medicine.

Buildings are mere shells without great men to give them life. Some were there when Winter came to Yale—L. B. Mendel, H. B. Ferris, S. C. Harvey, F. P. Underhill, C.-E. A. Winslow, and Arnold Gesell. Prof. Ross G. Harrison of Zoology was given an appointment on the faculty of the Medical School, as a token of the position of medicine as a branch of biology, and with the hope of furthering this fundamental concept. One of Winter's greatest contributions, and a tribute to his perspicacity in the choice of men, is the selection of the early faculty. Among those who came and remained throughout their careers were F. G. Blake, J. P. Peters, G. F. Powers, and A. H. Morse. Their work is a tribute to the "full-time" system under which they served. As early as 1922 it was possible for the Dean to report: "Now more of the major clinical divisions of the Yale School of Medicine are on a solid and comprehensive full time basis than in any other School of the world." But then as now the full-time system had its problems. In 1931 he wrote:

> Money plays too heavy a role in present day affairs to be ignored, and a man serving more than one master for monetary reward divides his time and energy and all too frequently may give only the skimmed milk of his thought and ability if that, to the University, while enjoying the prestige that goes with his position, and using his University salary as pin money. The existence of such a condition will be a deterrent in seeking good men for academic fields. . . . Universities must recognize these facts. They must dignify important positions, and so reward desired men that the business of education comes to hold a place in the eyes of the world commensurate with its importance in society.

Men like the great clinician and former Dean, George Blumer, although engaged in active practice, gave loyally of wisdom and time, and continued to inspire generations of students. Winter fully appreciated the importance of such part-time teachers, as a supplement to the solid core of a full-time staff. In 1935 he wrote: "There should be no 'ins' and 'outs.' The full-time

man has one contribution to make and the part-time man has another, but one is not necessarily superior to the other."

In carrying out the arduous tasks of his deanship Dr. Winternitz cherished and freely acknowledged the help he received from two brilliant and immensely efficient ladies, Miss Miriam K. Dasey, as Registrar, and Miss Lottie G. Bishop, as Executive Secretary.

THE GREAT IDEAS

Clearly, it was not merely the charm and persuasiveness of the suppliant, but also his great ideas that succeeded in obtaining the wherewithal for the new school.

The Yale Plan. Among his greatest contributions is undoubtedly the Yale Plan of medical education. The worth of this contribution is based not so much on the novelty of the individual elements in the plan as in their combination, and most of all in the courage that put them into effect. According to Dean George Blumer, Yandell Henderson as early as 1906 advocated "horizontal" rather than vertical teaching; Harvey Cushing had remarked on the possible merits of departing from the rigid, established curricular sequence and permitting students to study some of the clinical before the laboratory disciplines; the thesis had long been a requirement for the M.D. degree at Yale, as in many European schools of the 19th century. Now these things and others were vitalized and truly implemented. The loyal support of such true practitioners of freedom as John Peters and Samuel Harvey assured the success of the plan.

The attitude of the new Dean is reflected in one of his early Annual Reports (1921-22): "Indeed a small medical school as a part of a great University like Yale is particularly well adapted to pedagogical experiment, and it is hoped that such experiments, judiciously carried out, will be one of the means by which this school will aid medical education and give character to itself." One of the first steps was to make the curriculum more liberal: "It is only necessary here to point out that the policy of the School of Medicine is to eliminate unimportant and subsidiary sections and to put its strength into the fundamental sections of the School" (1920-21). Again these words are timely, for unfortunately recent years have seen some erosion of this policy, and minor specialties have been permitted each to intrude a caricature of itself into the students' time. The need of the undergraduate in medicine not only for a basic core of principles but also for freedom to develop according to his interest and abilities cannot be supplied by pious words, but only by giving him that most precious of all quantities—time. To this end action was taken, and the Dean could state in July of

1922: "A total of 1208 hours, the equivalent of one year's work, has been salvaged from the required courses," and: "Further changes in the curriculum have been made in an attempt to correct the overcrowding and offer to the student the opportunity to exercise his individuality." The first great step, then, was truly to provide opportunity for elective study and for the priceless experience of a close association in the laboratory with members of the faculty in the preparation of the thesis. On the latter point he once remarked: "The most that can be done is to put the student into the proper atmosphere, to provide opportunity, and to place a premium on research."

Gradually, "the liberalized curriculum modeled after the accepted plan of graduate instruction has been put into successful operation." Medical students were considered mature graduate students in the fullest sense. The principle was to provide opportunity for acquiring a broad background in human biology during the first two or more years in the School of Medicine, without excluding the possibility of working in other schools of the University. The choice of whether to continue into clinical medicine or to work toward the Ph.D. degree was to be left until the end of this period. Artificial barriers between students and faculty, such as the vicious system of attendance taking and grading in individual courses, were abolished. The principle is epitomized in Winter's memorable words: "Universities should be interested primarily in providing opportunity for learning and not in giving instruction. Teaching need enter only insofar as there is failure to learn."

The student was to present himself for examination for admission to the clinical departments when he considered himself ready, and the examination was to be given by the clinical faculty, rather than by his teachers in the preclinical years. Deviation from traditional patterns was encouraged, especially if the student had previously done advanced work in some special discipline. Thus, some students were encouraged to take the course in Pathology during the first year, before they had studied Anatomy. This not only made them acutely aware of their ignorance, but increased the stimulus to relieve it. Some feared that this system would make for laxity in study. Actually what was expected of the student under the Yale System was more rather than less. The great majority of students treasured their new-found freedom, thrived spiritually and intellectually, and were encouraged by this new self-discipline to become scholars in medicine throughout their lives.

The Yale System was fully in operation by 1926, attracted wide attention, and was hailed by such influential teachers as Charles Stockard of Cornell. He wrote: "The country at large owes its thanks to the faculty of the Yale Medical School for having taken a definite step in what is probably a very wise direction. It is at least gratifying that one school should have asserted

its individuality and independence by introducing a really different system, rather than simply following through the stagnant style of addition and subtraction, as applied to the several courses in the Medical College." Its best features have been widely copied under one or another name, with great benefits from a fresh advertisement to its new heralds, who often acknowledge not their borrowings.

Then as now, it served as an incentive to many of the best young minds to seek admission to this School. Great pains were taken by the faculty in the selection of students and in this process the Dean himself played a dominant role. He picked them by ear, chiefly for some peak of interest or performance rather than for a high level of mediocrity. Although occasionally one proved to be off key, most made good harmony and were receptive to the inspiration of the great faculty of those days. The aim of this careful process of selection was to assure that none admitted would fail. Consequently, the atmosphere was one of scholarship, not mere competition for grades.

Over the years the Yale plan has been repeatedly re-examined and reaffirmed in the place of its origin. By and large it has resisted the gnawings of those with less faith and imagination than its originator, and it has been an inspiration both to students and faculty.

Group Teaching. The idea of "vertical" teaching appealed to Dean Winternitz and is discussed in his report of 1920-21: ". . . We believe it would be practicable and advantageous to develop what may be termed group teaching along interdepartmental, as well as intradepartmental lines." He knew, however, that excessive formalization would inevitably result in formalinization, and he said "Every effort must be made not to stifle the opportunity for learning by building up a great machine for teaching." The "salvage" in time from the required courses could thus be used in productive, preferably independent, scholarship.

An early expression of this concept was the "Conference Committee for the Study of Neurological Conditions" that formed in 1923 on its own initiative. At first it consisted of four members from various departments. From this grew the larger and even more representative Neurological Study Unit that was ably directed for many years by Prof. Harold S. Burr and which still flourishes. The aims of the Unit were to extend and disseminate knowledge of the central nervous system by providing contact among persons interested in its various aspects, from this school and elsewhere, to stimulate interest and investigation on the part of students and faculty, and to aid in the care of patients with neurological disorders. Other units with similar aims sprang up such as those concerning themselves with the cardio-

vascular system, arthritis, and, more recently, gastroenteric diseases, genetics, and the sociological aspects of medicine. They have had an important function, not only because they represent a spontaneous and flexible instrument of instruction, but also because they have served to reduce barriers among departments and have emphasized the true unity of the various disciplines.

"The Proper Study of Mankind." Like that other great pathologist and humanist, Rudolf Virchow, Dr. Winternitz saw the patient not as a "collection of diseased organs," but as a human being buffeted also by stresses of family and society. These he recognized as capable of influencing, or even initiating, disease. His interest in preventive medicine was evident in his very first report as Dean, and this was shortly thereafter even more emphatically formulated: ". . . that preventive medicine shall be so incorporated in all clinical teaching that it becomes a basic principle for every graduate of the school" (1922-23). This attitude has continued to permeate medical teaching at Yale.

From the first he alerted the Yale Corporation to the imperative need for establishing a section on psychiatry. As early as 1921 a bill was introduced into the State Legislature which asked for the establishment of a psychopathic clinic in New Haven, and for the privilege of utilizing it for instruction of medical students. When this proposal met with defeat, he did not yield to discouragement, but rather raised his sights and mounted an intensive and ultimately successful search for support. Arthur H. Ruggles, who rendered valuable service in teaching psychiatry in this school during the interim, recounts how the Dean's concepts broadened to include the total study of man in society. The search for a chairman in psychiatry was pressed first in this country, and then in a visit of several months to various centers abroad. This resulted in the appointment of Eugen Kahn to the first full-time chair in psychiatry.

Perhaps the broadest, most challenging, and most farseeing of his ideas was that of the Institute of Human Relations. The first inkling was given as early as 1926 ". . . the acceptance of a policy that should be far-reaching, to bring into geographic continuity, probably in the same building, the various sciences associated with behavior, chiefly human behavior; . . ." To conceive of medicine as a social science ". . . demands cross fertilization by a variety of disciplines never before considered in conjunction with medical education." Increasingly he stressed that "The social sciences must play an ever increasing role in the training of physicians, lawyers, ministers, and indeed all who have to do with men and the many complex conditions governing their lives and happiness."

The vision came into sharper focus as it was contemplated from every aspect in the good company of another great Dean, Robert Maynard Hutchins of the School of Law, and of a great president, James Rowland Angell. Interest and enthusiasm were generated throughout the University. *Yale Proposes to Study Man* was the title of a brochure that described its scope. According to plans announced in 1929, the Human Welfare Group in New Haven was to include not only the New Haven Hospital and Dispensary and the Schools of Medicine and Nursing, but also an "Institute of Human Relations."

The Institute was not to be a "School," but a physical setting for the voluntary association of certain arts and sciences dealing with human life. The Dean's prospectus stated: "No less stress need be put upon the production of scholars and the discovery of truths, but more emphasis should perhaps be placed on what these scholars and truths may contribute to the general weal." This was the theory on which the Human Welfare Group was based. Above all the new Institute was to provide the opportunity for vastly increased communication and cooperation. He expressed the hope that: "As the methods of cooperative research are developed, it should be possible to obtain new and important facts regarding the causes of major human maladjustments, such as physical and mental disease, crime, divorce, and unemployment." Dean Hutchins, and his successor, Charles E. Clark, saw the law not merely as the study of a collection of arbitrary rules, but as an instrument of human welfare, and that this instrument could not be used without an understanding of human life. Winter envisioned the ultimate introduction of a Department of Clinical Sociology into the School of Medicine: "The aim is to make every medical student think always of the individual as a psycho-physical entity, no part of which can be dealt with satisfactorily except with due consideration of the other factors." He also put this into more homely and picturesque language: "The old fashioned doctor, who was not a specialist, but who knew all about your passion for fishing, who always asked about your son Billy, and who carried away most of your troubles in his little black bag has become a dim figure on the horizon." It was to recapture some of this understanding of man in the setting of his family and community that was again considered of prime importance in medicine. On the other hand, the plan of the Institute acknowledged that the problems of sociology required for their solution aid from the biologist, the psychologist, the doctor of medicine, and the jurist.

As the plans crystallized, munificent support, in sight of the $8,000,000 required, was provided by the Rockefeller Foundation, General Education Board, and Commonwealth Fund. This included not only $2,000,000 for

the building itself, but a maintenance fund for a Psychiatric Clinic, and endowments for the Departments of Psychiatry and Mental Hygiene, for Sociology, and for Psychological Research. The Institute was duly dedicated on May 9, 1931 amidst fanfare, with speeches by President Angell, Governor Wilbur Cross, the distinguished erstwhile Dean of the Yale Graduate School, Dr. Ray Lyman Wilbur, then Secretary of the Interior, and Mr. G. E. Vincent, the former President of the Rockefeller Foundation. Housed in the new building was the recently established Department of Psychiatry, in the planning for which the idea of the Institute had been conceived. This included space both for research and for the care of a small number of psychiatric in-patients. Magnificent quarters were also provided for the Child Study Unit which had already been functioning actively under Prof. Arnold Gesell for more than fifteen years. Office and research facilities also now were available for the Graduate Departments of Sociology and Psychology. Drs. Walter and Catherine C. Miles were invited to come from California to add strength to an already strong faculty in basic psychology. It was planned that cooperation would be given by sections on Neuroanatomy and Neurophysiology, the latter established by the appointment in 1929 of Prof. John F. Fulton, and further strengthened by the addition in the following year of Prof. J. G. Dusser de Barenne, previously of Utrecht. Contributions were also expected from psychobiology under Prof. R. M. Yerkes. To further the work of the last mentioned and his group, a Tropical Anthropoid Station had been endowed at Orange Park, Florida.

It is of interest that one of the first cooperative studies to be carried out by members of the Institute dealt with juvenile delinquency and its determinants within the family. Others concerned themselves with human problems of industry and with factors in unemployment. Studies of this scope were distinctly within the purview of the Institute, and it was anticipated that economists and members of the Schools of Law and of Divinity would ultimately participate.

The greatness of the idea embodied in the Institute is no less at a time, 25 years later, when the maturity of these disciplines and of the capacity of their practitioners to collaborate has not yet allowed this proper study of mankind to be more than begun.

Dentistry as a Branch of Medicine. To Dean Winternitz dentistry was a branch of medicine. On the one side he realized that a knowledge of the dental structures could be a valuable part of the education of the physician; on the other, teaching dentists to recognize in the course of their work the manifestations of diseases other than those of the teeth was clearly desirable

as an important measure of preventive medicine. Further, the biology of the dental structures required, as it does today, intensive investigation.

To meet these needs, an Oral Pathology Unit was organized, again with generous support from the Rockefeller Foundation. The collaboration of the Departments of Medicine, Surgery, Radiology, Bacteriology, Immunology, and Pathology was enlisted. Scholarships to the School of Medicine were provided to students of superior ability who had already acquired degrees in dentistry, and who were expected to engage in appropriate investigative work. Drs. B. G. Anderson and C. G. Burn played important roles in the leadership of the Unit which was productive of original research of a high order. Many of the recruits to this Unit such as Burket, Weisberger, and Arnim subsequently assumed important chairs in schools of dental medicine. Toward the beginning of the Second World War, after Dr. Winternitz' retirement as Dean, this liaison between dentistry and medicine at Yale was, to his regret, permitted to lapse, but he always retained a hope of its revival.

Nursing as both Science and Ministry. Having mentioned the need for a superior school for nurses at Yale in his first report as Dean, Dr. Winternitz two years later was somewhat apologetic but no less convinced: "This is hardly a subject to be included in the report of the School of Medicine, but it is felt that the establishment of a School of Nursing is of such moment to the School of Medicine that a word of appreciation is not out of place." Not only would a better background in science immensely increase the usefulness of the nurse in the conduct of medical investigations on the wards, but her own contribution to the care of patients would be improved if she were better prepared to comprehend ". . . the community as well as the bedside aspects of disease." Furthermore, in such a School, Dean Winternitz saw the opportunity of making a fundamental contribution to nursing education in this country, especially in the development of future teachers and administrators in nursing.

On April 25, 1923, President Angell was able to announce the creation of the first School of Nursing as a school of a university, with its own dean, faculty, and budget. Enrollment was to be limited to selected college graduates. The appointment of Miss Annie W. Goodrich as Dean was most fortunate. She had already demonstrated her ability as an outstanding leader in nursing education at Johns Hopkins, where Dr. Winternitz first came to know her, and in her positions at Columbia University and the Henry Street Settlement in New York City from which she came to Yale. Under her direction the school soon reached the desired level of function and came to serve as a model for schools in other universities and hospitals to which it in turn supplied distinguished leaders.

PARTICIPATION AND CATALYSIS IN SCIENCE

A second birth as an investigator, an event so rare as to constitute a *nova* in the medical firmament, occurred when Dr. Winternitz retired from the deanship in 1935. Clearly, the demands of that office could not have been met as they were without serious interruption of a productive career in pathology. After 15 years as a preoccupied administrator whose desk covered the country, he turned to an early interest in vascular and renal disease. Old methods were applied with new vision and with unprecedented vigor. Many remember well his infectious, even roaring, excitement as each new injected and cleared preparation disclosed some previously hidden nugget of fact or insight. The remarkable vascularity of tissue surrounding atheromatous plaques was disclosed. A role of hemorrhage in the progress of these lesions was made clear, and important observations were made on mural hemorrhage as a mechanism for coronary occlusion. Further, it was discovered that loss of elasticity of the aorta was a sequela of age and relatively independent of the degree of sclerosis. This work was published as a monograph, *The Biology of Arteriosclerosis,* in 1938 with Robert M. Thomas and Philip LeCompte, a former student in this School. Studies of vascular disease had only begun with publication of this volume and they were continued with unremitting energy in subsequent years with the collaboration of Waters, Katzenstein, Mylon, and others.

During World War II, despite staggering national administrative burdens and a serious illness, Dr. Winternitz was able to direct a series of important studies on the pathology of shock.

In all of this work he was a direct and personal reagent in many colorful and sometimes violent reactions, but he also catalyzed many others that suggest clairvoyance of the future. Work in radiation biology, more specifically the effect of x-rays on enzymes, was carried out in the late twenties by Drs. Hussey and Thompson. His interest in dental medicine, and in those disciplines embodied in the Institute, has already received mention.

After his return to the Department of Pathology, and especially in the post-war years, the availability of powerful new tools for the basic sciences had greatly increased the research potential of pathology. Clearly, then, the modern department conceiving of pathology broadly as the study of disease by functional as well as anatomical methods required a group of men with diversified experience and competent to use the new tools to good purpose. Consequently, sections in the department were established which emphasized chemistry and physiology as applied to the pathology of the circulatory and respiratory systems, histochemistry and electron microscopy, blood coagulation, and experimental cancer. Winter was convinced that the best teaching comes when the teacher is personally involved in investigating the subject

he is teaching. The time of the universal "authority" in pathology has long since passed. This tradition in the department has been maintained.

If his scientific interest in cardiovascular-renal diseases may be considered one of his vocations, then the problem of cancer ranks high among his lifelong avocations. The term "avocation" is used advisedly because Dr. Winternitz had no personal preoccupation with cancer research. He was not an investigator in the field and perhaps for this very reason was able to bring his almost unique qualities as a medical scientist and a medical administrator to bear on the problem in an idealistically objective way.

In 1933, together with Dr. Samuel Harvey and Dr. George M. Smith, he was instrumental in establishing the Atypical Growth Study Unit at Yale. This was a necessity in a setting where heretofore activity in cancer had been limited largely to clinical considerations—surgical pathology, surgery, and radiation therapy. The Study Unit included chemists, geneticists, biologists, as well as those interested directly in clinical cancer. The very name—"atypical growth"—is indicative of Dr. Winternitz' conception of the basic pathological process of cancer. He always assumed neoplastic growths were merely variations of physiological growth and that what is known of one would be important in the understanding of the other. With this concept, the conventional research tools of morbid anatomy and of histology were limited, and Dr. Winternitz turned towards fundamental biochemistry as the broad base on which to build a productive approach. Throughout the rest of his life he never varied from this point of view. Developments in the field seemed to support him at every step. Identification and concentration of the carcinogenic hydrocarbons in tar, the discovery of the cancerogenic azo dyes, the description of chemical organizers in embryonic tissues, and knowledge of the relation of steroid hormones to the genesis of cancer all occurred shortly before or at about this time. Through the generosity of the Anna Fuller Fund under the Directorship of Dr. George M. Smith, such men as Ernest L. Kennaway, Joseph Needham, A. Lacassagne, and T. Yoshida, among others, not only lectured at Yale but consulted with those interested in cancer research. During this period Dr. Winternitz was on the alert for men. Allen and Gardner in endocrinology, H. S. N. Greene in transplantation biology, Leonell Strong, the geneticist, and Francisco Duran-Reynals, the virologist, came to New Haven.

A most important result of the establishment of the Atypical Growth Study Unit, both for cancer research at Yale and for cancer research at large, was that it in part influenced Mr. Starling W. Childs in 1937 to locate The Jane Coffin Childs Memorial Fund for Medical Research in Yale University. This magnificent gift of a capital sum of over $3,000,000 designated specifically for cancer research was given to Yale in trust to be

used in the support of cancer research at Yale or anywhere in the world upon the recommendation of the Fund's Board of Scientific Advisers. At the time, before the availability of the present huge sums from the Federal Government, the Childs Fund loomed large and played an important role in the awakening of scientific, lay, and governmental interest in the attack on cancer. Dr. Winternitz was a member of the original Board of Scientific Advisers and in 1948 Dr. Winternitz succeeded Dr. Stanhope Bayne-Jones as its Director. He was superbly equipped to guide the Fund toward the idealistic objectives required by the distinguished scientists on its Scientific Board. When Dr. Winternitz became Director, the Fund, with the advent of huge governmental and public resources, was no longer one of the largest granting agencies in the field of cancer. On the other hand, as a private fund, it suffered from few rules or restrictions. Its history under Dr. Winternitz has reflected this freedom. Two convictions guided him and his Board during this period: first, that a broad base of fundamental medical knowledge must be built before dramatic applications can be achieved in the field of growth and, secondly, that the generous and long-range support of investigations of top-grade men, constitutes the most effective use of a comparatively small research fund. A list of the scientists whose work has been supported by the Fund reads like a small "Who's Who" in basic medical science. As was characteristic of Dr. Winternitz, the emphasis was always on men with ideas, on men with new techniques, and above all on men who were dedicated to the constant work and thought that beget ideas and correlations essential for progress.

One thing more: Dr. Winternitz had no magic word for the eventual control of cancer. Nor did he crusade necessarily to save mankind from this scourge. He was interested in cancer research for its own sake, particularly as a fascinating subject which increases basic knowledge of life mechanisms. As a medical problem for attack he saw great opportunities for development of knowledge in the fields of biochemistry, chemical genetics, surgical pathology, in radiation biology, and in the clinical care of cancer patients. Men with comprehension of both basic and clinical aspects, he knew, are urgently needed if progress is to be made. Ways and means of expediting this progress were his chief concern when time, and time alone, forced him from the scene.

NATIONAL SERVICE

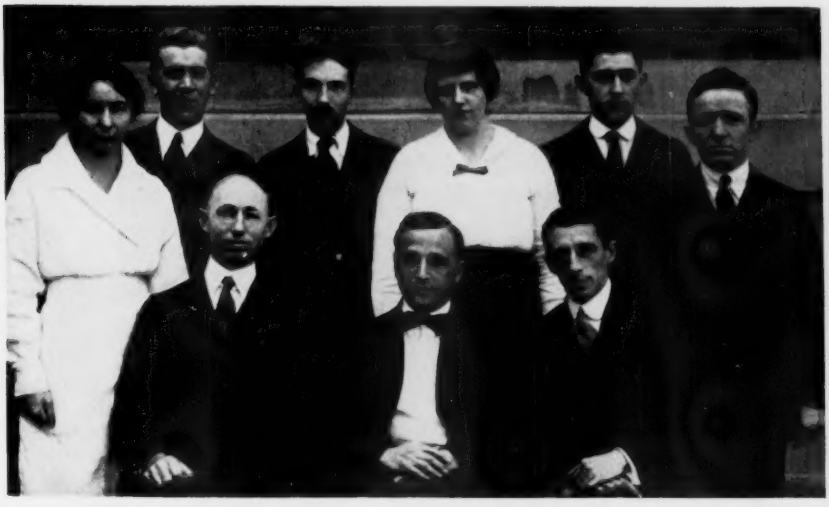
Winter's organizational and scientific talents were, naturally, brought into service in both World Wars. Having fathered the Biological Section of the Chemical Warfare Service in the First World War and finding, as he put it, "only a dried-up kernel," at the beginning of the Second he grew from

this the large and important new laboratory at the Edgewood Arsenal. This was facilitated by his position from 1941 as Chairman of the Committee on the Treatment of War Gas Casualties of the National Research Council and after 1944 as Chief of Division Five (Chemistry) of the Office of Scientific Research and Development.

It seems strange that these activities should have furthered Dr. Winternitz' association with cancer, but this was in fact the case. Among the subjects under intensive study by various groups were the systemic effects of mustard gas, and particularly those of an analog of mustard gas, "nitrogen mustard." During the first World War mustard gas was noted to destroy lymphocytes and the lymphoid tissues of experimental animals. These facts came to the attention of several workers in the field including Drs. Alfred Gilman and Louis Goodman in the Department of Pharmacology at Yale. The earlier observations were confirmed, and Gilman and Goodman recognized that the nitrogen mustards might have potential as chemotherapeutic agents in lymphosarcoma and allied diseases in man. After preliminary experiments with leukemic mice, the first clinical trials carried out in the Department of Surgery at Yale resulted in dramatic temporary regressions of the tumors, but also indicated the inherent toxicity of the substances being tested. The potential importance of the nitrogen mustards for civilian medicine was indicated by these trials. Information about them was to be disseminated impartially to centers for civilian cancer research and yet the secrecy that surrounded these substances as warfare agents needed to be guarded. Dr. Winternitz, under the aegis of the governmental research agencies concerned and the Jane Coffin Childs Fund, organized a meeting on July 1, 1944 of all interested groups at which disclosures to civilian medical centers were made and plans for comprehensive study of these agents were outlined. Certainly the recognition and development of the nitrogen mustards as chemotherapeutic substances in malignant disease was an important early factor in the enormous growth of this phase of cancer investigation.

Although he returned to New Haven in the period after World War II, Dr. Winternitz remained active in the National Research Council. From this vantage point he continued to foster the study of cancer. The Committee on Growth of the National Research Council was founded in 1946 largely on his initiative and he became its Chairman in 1948. One of its most useful activities over a period of years was the evaluation of applications for grants-in-aid for the American Cancer Society. The study panels for this arduous task were expertly organized by Dr. Winternitz and his associates and through this work he came into direct contact with outstanding scientists in each phase of the field. During this period at the National Research Council he also served on the Subcommittee on Oncology. One important problem

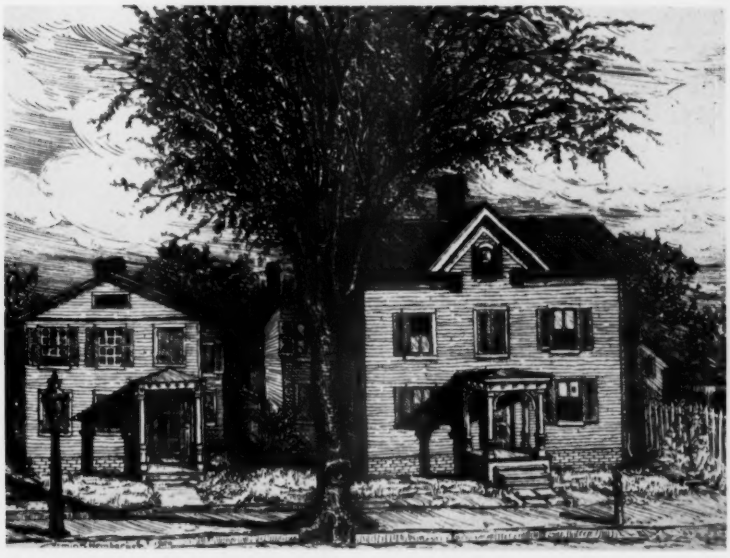
Above: Staff of the Department of Pathology at Johns Hopkins in 1917, just before Dr. Winternitz came to Yale. He is seated next to Dr. Welch. At the left end of the second row is Dr. Stanhope Bayne-Jones. Dr. R. J. Hussey, who later became a Professor of Pathology at Yale, is shown behind Dr. Bayne-Jones.



Dean Milton Winternitz with the Pathology Staff at Yale in 1921. In the first row are Drs. R. A. Lambert, M. C. Winternitz, and G. H. Smith, later Professor of Bacteriology and Immunology and founder of *The Yale Journal of Biology and Medicine*. In the second row are Drs. Isabel Wason, F. P. McNamara, a co-author of *The Pathology of Influenza*, Dr. E. S. Robinson, Dr. Helen M. Scoville, Dr. E. O. Boggs, and Dr. T. S. Moïse. It is of interest that Drs. Wason, Scoville, and Moïse all assisted Dr. Winternitz after World War II, in his work with the National Research Council, after distinguished earlier careers of their own.

'Neath the Elms

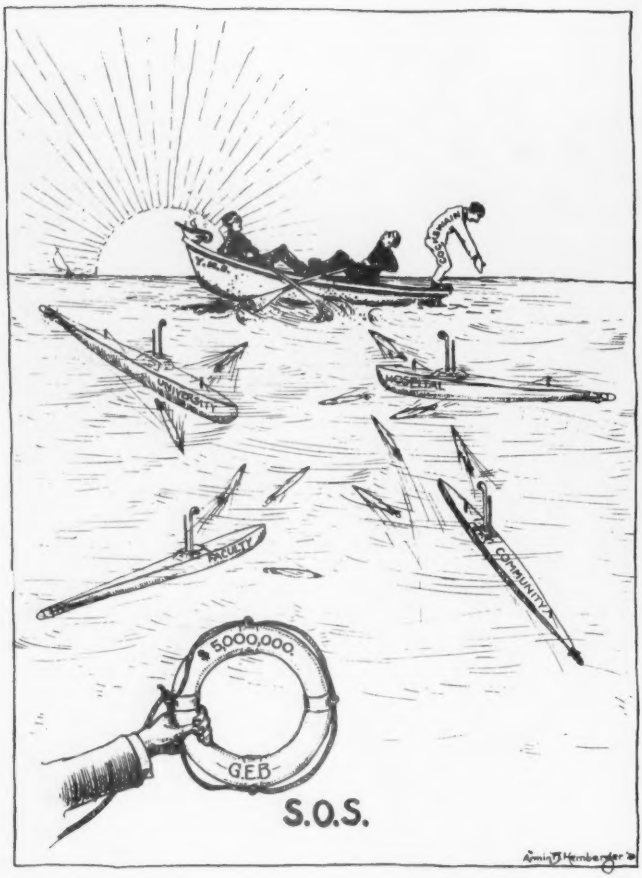
Anatomy at Yale, 150 York Street, until 1923. This building, formerly a dwelling, housed the entire Medical School from 1860 to 1907.



'Neath the Elms continued

Above: Laboratories of Surgery, Medicine, and Obstetrics and Gynecology, on the site of the East Wing of the Sterling Hall of Medicine. These quarters were in use from 1907 until 1920 when Dr. Winternitz became Dean.

Below: The "Barrack." This wooden structure on the corner of Congress Avenue and Cedar Street was erected to house the Yale Army Laboratory School shortly after Dr. Winternitz' arrival in New Haven. The first wing of the Anthony N. Brady Memorial Laboratory, just completed in 1917, is at the right.



The eloquent cartoon sent to Doctor Flexner of the General Education Board by the new Dean in lieu of a detailed statement of the needs of the Yale School of Medicine as of 1920.

Three Deans, 1935. Dr. Winternitz had retired from the Deanship earlier in the year and is wearing his laboratory work suit under the dark coat. His predecessor, Dr. George Blumer is at his left, and his successor, then in office, Dr. Bayne-Jones, is at his right.

Dr. Winternitz has the floor at a dinner, *circa* 1950. Above, the penultimate of a series of self-evident truths is uttered. Below, an inescapable conclusion is reached. Dr. Bayne-Jones is an attentive listener.

facing the group was the necessity of disseminating up-to-date knowledge on the surgical pathology of tumors to practising pathologists. Dr. Winternitz had the background to deal with this problem. Earlier, near the end of the war, he had had prepared a series of present status reports on Chemical Warfare Medicine by investigators in the field. This was published as the Fasciculus on Chemical Warfare Medicine. He now stimulated the preparation of a comprehensive series of fascicles on the biology of tumors in man. Some 25 to 30 sections have already been published. With others that are appearing, these comprise the magnificent *Atlas of Tumor Pathology*. In no other way has so much essential knowledge of tumor pathology been made available to pathologists dealing directly with doctors and patients. These fascicles are distributed throughout most of the world and are forming a basis for discussions on the establishment of an international standard for tumor nomenclature. If the individual fascicles of the Atlas can be kept up-to-date by periodic revisions and additions as Dr. Winternitz hoped, their value will be continuing. Indeed, it would seem necessary that cancer research agencies recognize their responsibilities in this regard.

Another Committee established at the National Research Council was the Committee on Cancer Diagnosis and Therapy. Dr. Winternitz, in organizing this group, recognized the need for a knowledgeable body to protect the public from false claims of cancer "cures" and from cancer "quacks," and at the same time to review all claims of cancer cures so that nothing of possible merit would be overlooked.

The United States Committee on the International Union Against Cancer was also established under Dr. Winternitz' direction in 1952 to serve the American agencies interested in cancer in their representation in the International Union Against Cancer. The United States Committee has subsequently played a significant role in the development of world-wide researches on cancer epidemiology and encouraged exchange of significant information on cancer investigation and control.

Dr. Winternitz continued to be concerned with detection of biologically active chemical substances, particularly those that might possess cancericidal activity. Moreover, it was clearly important to preserve, maintain available, and disseminate information as it was acquired. This led to the establishment at the National Research Council of the Chemical-Biological Coordination Center and to his service as Chairman of its Advisory and Executive Committee.

When he reached Emeritus status in 1950, his undiminished energies found an outlet in the Chairmanship of the Division of Medical Sciences of the National Research Council. Among his more important activities in this capacity were the renewed development of the National Blood Program and

the creation of the Medical Sciences Information Exchange. When he retired from the Chairmanship of the Division in 1953, he continued as a member of the Executive Committee and of several advisory groups. He served also as a member of the Hoover Commission and continued vigorously as Director of the Childs Fund.

Official recognition of his services came after World War II in the form of the King's Medal for Service in the Cause of Freedom, and the President's Certificate of Merit. The University he served so well honored him with a Yale Medal and a Doctorate of Laws in 1952.

WINTER IN PERSON

An unforgettable image remains of Winter in the 1930's, in the days of his greatest striving and fulfillment. He was small yet overwhelming; dark and brooding, yet shining and sprightly. Always he was in motion. His deep brown eyes surmounted by mobile, expressive brows, were his most arresting feature. They could remain veiled, turn evasively away, indicate astonishment with no hint of whether this was real or feigned, pierce into one's soul, or soften with sympathy and concern. His glasses were used less for vision than to be twirled like a propeller to give the desired speed to his utterances. His voice was loud and clear, in fact often ringing, but he could purposely sink it to a whisper—the more to capture attention. He used its tone, even better than well-chosen words, to convey nuances of meaning. His laugh was gay, sometimes mocking, and he could use a chuckle to reinforce a point or increase, or reduce, a verbal sting. He was severe but full of humor; ruthless but tender. Many of the host whom he helped and befriended never knew it. In his headlong course he made enemies, but gained many more devoted friends. He was a theater of opposing forces and molded by his moods, yet he resisted them, and few knew his innermost thoughts until he was ready to reveal them, obliquely or directly.

Winter was an electrifying teacher. To teach was to stimulate, not to regurgitate well-recorded facts. Lectures he considered an abomination, but he did not quite dare abandon them. His own were never dull, although they might depart widely from the topic. When he considered a subject important and not well explained elsewhere, they were models of color, clarity, and force. Then his students remembered forever what he said as well as how he said it. He was at his best in what he liked to call "gross morbid." Often these sessions were a little of both. The arena was the grey-tiled, terrazzoed Large Autopsy Room, a chamber of great dignity which was always swept and polished by the loyal and devoted Frank Fousek and his aides. On its wall was inscribed: "Hic locus est ubi mors gaudet succurere vitae." This was freely translated by the students as "This is place where death makes

suckers out of the living." The Lion entered promptly at the appointed time by a small door. The illusion was heightened by his coat of a tawny orange hue and by a restless pacing up and down. After an ominous silence, the victims were presented with the specimens of the day. The object was to make them relax their grasp. He was impatient of ignorance and intolerant of stupidity. He had, also, a fine nose for detecting dissimulation and if he caught even a hint of that aroma, the fur and even assorted viscera would fly! If the student could defend a reasonable position with clear and independent reasoning against the alternatively browbeating or wheedling attacks, there might even be a hint of praise in the subsequent roar!

No one knew better how to transfix attention than this master. Each student was aware that before the opening day his name had already become firmly attached to his face. This was generally considered to be simply another manifestation of second sight, although a few suspected that it may have taken a little secret study. These names were often preposterously garbled in a way to bring out some individual characteristic or a bit of personal history well known to the students' classmates, but known to the Dean, Heaven knows how! A favorite turn was to call the ladies by the names of their swains in the class and vice versa. Feelings were never hurt to the point of no repair. One student captured the spirit of the proceedings when he remarked that the Dean could "bite your head off with his tongue in his cheek." When the maulings seemed most brutal, each student still knew that Dr. Winternitz had a real personal interest in his welfare. He was never too busy to see a student. Best of all, each student knew that he had faith in him. Small groups were invited to his office to discuss over a cup of tea their problems and those of the school. One of his illustrious disciples, Max Taffel, tells how a group of students in the late twenties who had to work to support themselves during a part of the day asked permission to use the Brady Laboratory in the evenings and on weekends. In due course each was quietly presented with a key to the School itself! They thus became trusted participants in a great adventure. Small wonder that the Dean was deified!

Outside of his official contacts, Winter's behavior with the students was often less than formal. Many will recall seeing him driven to his home on Prospect Hill in an elderly "Model T" known as the "bathtub" for lack of top or windshield, in the midst of a crowd of students so large that there was standing room only on the running board. At parties he was gay, even boisterous, had a word for one and sundry, and hugely enjoyed his role as target in the students' skits.

In his own department, he was *pater familias*. Appropriate stimuli were applied and help was freely given when needed. There was never a Christmas without a party in the Staff Room on the top floor of Brady to which a

barrel of oysters arrived from Baltimore, to be washed down with a hogshead of the hardest cider from New Hampshire—product of the Chief's own brewing. To this the tender hams, good red beef, variegated salads and cakes were all incidental. In time these parties acquired an international fame. Visitors, no matter how distinguished, were welcomed with potent libations. To one such party a noted lady pathologist from Britain arrived with a very young and innocent male compatriot, who promptly lost contact with the world. Since the lady had urgent engagements elsewhere, he was left horizontally ensconced on an old leather couch in the care of a somewhat relaxed House Staff. The Chief always had the central function of distributing little gifts duly inscribed by the Staff to one another. Often unsuspected talents and hidden qualities were thus made public. Music was provided but varied with the talent available. The singing of carols, with variations, continued as long as voice would last. Somehow all survived to tell the tale, or many tales, when their heads had returned to normal size in the course of subsequent days.

Winter enjoyed a life with an active and always interesting family. His marriage to Helen Watson in 1913 gave him a delightful companion who was the source of needed spiritual sustenance in many early defeats. Of the five children of this marriage, one, named after his great preceptor of the Hopkins days, has followed the medical tradition of the family. Winter bore the terrible blow of his first wife's death with courage and in silence. After his marriage in 1932 to Pauline Webster Whitney, "Polly" to hundreds of admirers, he resumed a happy family life.

Dr. Winternitz spent his summer vacations, and those were usually from June 20th until after Labor Day, at his country place in New Hampshire. "Treetops" is situated high above Newfound Lake with a magnificent view of Mt. Cardigan in the western distance. In spite of being on the side of a mountain, the land is fertile and fine for gardening. Winter early became an expert gardener and landsman, with the advice of his two native helpers on the farm, Peter Sharon and Peter Weesul. Weesul, of central European origins, still survives, and after many years of both active and passive resistance to the boss, finally achieved a degree of dignity and autonomy seldom equalled in any of Winter's other associates. This was not without concessions, however. As soon as Peter Weesul had learned that the work day began at 4:00 a.m. and continued to dark, and that one did not get paid on rainy days or in the winter, all went well. In his turn, he was just as hard on Winter in matters of how much manure was needed, or whether the corn was ripe for picking, and the like. They remained devoted friends. Winter and Peter's gardening was, to say the least, macromegalic! Huge plots of corn, tomatoes, cabbage, broccoli, melons, etc. were put in each year, no

matter how small the entourage at "Treetops." This gave rise to many day-long canning sessions, participated in by whatever guests were on hand. These were presided over by Mrs. Winternitz, with running criticisms from "the Doctor" throughout the day. Other portions of the unused vegetables were taken to the village by Winter in an ancient truck or his old Buick roadster, and showered upon the villagers in great profusion. This occurred at the glut of the season. The townspeople nevertheless always received the produce because they were devoted to Dr. Winternitz and considered him a "character."

After years with the vegetables, Winter branched out more and more into flowers and before he died became an enthusiastic horticulturist. Not only were there acres of gladioli, asters, and pinks, but he developed his own private garden where he knew each delphinium, begonia, and tearose by name.

Dr. Winternitz did not confine his outdoor activity at "Treetops" to gardening. Chickens and turkeys were raised in regiments, but there was no sentiment here. Every pullet at the end of the season had her head chopped off and went into the freezer. The same fate extended to cockerels that had survived the onslaught of the grandchildren and guests during the summer. Cockerels is not correct, because Dr. Winternitz caponized every male bird on the place himself. When hormonal caponization came in, he was among the first to practice this successfully. Turkeys were raised in great abundance and scientifically at that. Kept on wire, they never touched the ground, and Dr. Winternitz was an expert at preventing black-head and the gaps. In the fall of the year, the excess poultry was slaughtered and brought to New Haven where it resided in the Pathology Department deep-freeze. Dr. Winternitz kept strict count of all birds placed in the freezer and whenever the house staff or a technician made off with one, he not only knew it, but somehow knew who the culprit was.

The summers at "Treetops" were gay, happy, and fun for all, with the added spice of the ever-present needling of the Professor. He did little scientific work in the summer, but much thinking. He had had built a small attractive cottage which he called his "laboratory." On the wall was a sign which said in Latin: "Here is the place where Summer finds Winter"!

While Dr. Winternitz had a great deal of interest in disease as it involves mankind in general, in his own person he treated it with annoyed contempt. Etiological agents of chronic bronchitis waged a continual battle against a doughty adversary, who with racking cough did his best to evict them over many years. In 1942, he suffered a coronary occlusion. He loudly denied this even as a possibility, resisted the necessary confinement, and escaped prematurely to his demanding duties in World War II. Years later he admitted

the validity of the undeniable evidence. A carcinoma of the tongue that was successfully removed in 1956 gave him more concern. The residua caused considerable pain and discomfort thereafter. His final illness was probably the consequence of recurrence of a duodenal ulcer that in the early twenties had been the source of a series of massive hemorrhages. Treatment by dietary means met with success, and the entire episode remained a well-kept secret. Two years before his death, symptoms that in retrospect appear compatible with duodenal ulcer, complicated also by the effects of a sliding esophageal hernia, reappeared. In the summer of 1959 he developed an anemia, and again massive intestinal bleeding. An operation disclosed multiple peritoneal abscesses, the source of which was not at once apparent. Despite valiant efforts to bring the situation under control, Dr. Winternitz died on October 3, 1959, to the sorrow of his many friends. The autopsy showed that a large duodenal ulcer had been the source both of the hemorrhages and abscesses. A well-healed myocardial infarct also was found.

Thus was lost to us a man who has left a shining intellectual heritage not only to medicine at Yale but to the World. Rarely have such true idealism, soaring imagination, surging energy, and fiery leadership been combined in one man, who was yet so humble. His dreams will be inspiration for the future. The words of Leonard Bacon spoken at the 250th anniversary of the founding of Yale fit no one better than Milton Charles Winternitz:

> "Of what was noble here, such words are weak.
> But a man of understanding put it thus:
> We do not make such men. Such men make us."

AVERILL A. LIEBOW, LEVIN L. WATERS

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GILBERT H. GLASER*

Section of Neurology, Department of Internal Medicine, Yale University School of Medicine

THE NEUROLOGICAL STATUS OF THE NEWBORN: NEUROMUSCULAR AND ELECTROENCEPHALOGRAPHIC ACTIVITY**

INTRODUCTION

During the past few years there has been a great development of interest in the neurology of the newborn and young infant, and many studies have been organized related to the evaluation of causes and early recognition of neurological defects leading to cerebral palsy, epilepsy, and mental retardation. This presentation will not be concerned with matters of incidence or causation but with a consideration mainly of the normal neurological status of the newborn. Suffice it to state that studies of incidence[1] indicate that at least 6 births per thousand develop these neurological defects. The actual incidence would be higher if mild disturbances could be determined, and the statistics do not include the number of neurological abnormalities incompatible with life. Among the basic causes of these disorders are primary developmental defects of the nervous system, natal trauma, and hypoxia. The mechanisms of edema, encephalomalacia, and neuronal degeneration are little understood. The significance of minor lesions such as fine degrees of edema, cellular degeneration, petechial hemorrhage, and small infarcts is not clear. A factor difficult to determine is that of the duration of intrauterine hypoxia prior to birth. Related to this problem of minimal lesion is that of the detection of minimal neurological defect in the newborn and young infant. This is important from the standpoint of diagnosis and prognosis, as well as the understanding of the mechanisms of development of epilepsy, the various disordered motor functions under the generic term of spasticity and cerebral palsy, and the defects in higher mental functions known as mental retardation. To this end, the neuromuscular and electroencephalographic activity of the newborn has been studied.

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* Associate Professor of Neurology and Chief, Section of Neurology.

** Portions of this work were presented at Seminars of the Neurological Unit, Harvard Medical School, Boston City Hospital, January 17, 1958, and of the Division of Neurology, Albert Einstein School of Medicine, New York City, March 18, 1959.

Aided by Grant B-2355 from the United States Public Health Service.

Received for publication October 28, 1959.

A NOTE ON FETAL REFLEX BEHAVIOR

Prior to considering the neurological status of the newborn, a brief statement concerning the development of fetal behavior may be worthwhile. Actually, there have been more detailed neurological studies of behavior of the fetus than that of the newborn. The works of M. Minkowski,[35] Windle,[80] and Hooker[11] have been most pertinent. Hooker found that the earliest reflex movement of the fetus is in the eighth gestational week. At this point in the development of the brain the beginning lamination of the cerebral cortex has started, but the external granular layer is just detectable. This reflex behavior is undoubtedly not related to any cerebral cortical functioning. By 14 weeks practically all of the neonatal reflexes may be seen in the fetus. Stimulation of the nose-mouth area (exteroceptive reflexes) activates specific responses around the area stimulated. Individual movements of body parts occur spontaneously in contrast to the earlier total body responses. The structural counterparts of the reflex behavior of the fetus are probably in the mid-brain and lower segments. Pathways to the mid-brain, but not significantly higher, are myelinating up to the time of birth.[9, 19] At 15 weeks there is some evidence of maintained finger closure or grasping, and even the abdominal muscles may contract in a weak abdominal reflex. At 25 weeks a fetus has been observed to have a Moro reflex. Most of the responses are developed by 27 weeks.

THE NEUROLOGICAL STATUS OF THE NEWBORN

At birth the human infant has a well-developed brain up to at least the mid-brain level but not the higher cortical regions. Conel[8] has described thoroughly the structure of the cerebral cortex of the newborn human. The cytoarchitectural pattern is established but is not well developed. Of great interest is the absence of formed Nissl bodies in the cortical neurons. These are present in the neurons of the brain stem and the spinal cord of the newborn. Similarly, there are no neurofibrils except in the large Betz cells. The precentral area neurons have the most differentiated dendrites. There appears to be body part localization early in the development of the motor area and this relates very definitely to the neuromuscular activity of the newborn child. The greatest maturity in this newborn cortex is in the region related to movements of the upper extremities, trunk and shoulder girdle, then the lower extremities, followed by the hand and head structures. So-called synaptic structures are minimal. Conel[8] saw "thorns" only on dendrites and cell bodies. Myelin is minimal in the cerebral cortex and insula, rhinencephalic and deep cerebellar nuclei. There are some vertical and horizontal fibers in the occipital lobe.

The most complete correlated studies of chemical, especially enzymatic, and functional patterns in the developing brain have been those of the guinea pig by Flexner and his group.[8] Activity in the cerebral cortex, both spontaneous and evoked, makes its first appearance only after a certain critical period of development has elapsed. This critical period in the guinea pig is between 41 and 46 days of gestation. The total period of gestation is about 66 days in this animal. The critical period coincides with the development of nerve cell processes especially in the cortex, the appearance of Nissl bodies in the neurons and the termination or mature point of development of the nucleus of the neuron. Biochemically,[8] this period also is at the time of maximum increase in the activity of cytochrome oxidase, succinic dehydrogenase and apyrase, and the time at which nerve cells become permeable to sodium. However, there are exceptions to this timing of enzymatic changes. Cholinesterase rises progressively and not suddenly, particularly after the 35th day. The acid phosphatase level remains constant in the fetal guinea pig cortex and falls after birth.[8]

In guinea pigs there have been observations that reflex movements of the foreleg and neck can be elicited by the 31st day, those of the fingers and toes on the 35th day, of the jaw on the 38th day.[8] This is of interest because these reflexes appear before cortical stimulation is effective and before electrical activity of the cortex is observed. This would mean that these reflexes probably are mediated subcortically. However, by the 42nd and 45th days, movements of the extremities and head structures may be obtained by cortical stimulation. Both Jasper[17] and Flexner[9] found that rhythmical electrical potentials could be obtained from the cortex of the fetal guinea pig at about the end of this critical period for cellular differentiation and chemical changes. These potentials in part arise from the cortex itself and not wholly from the underlying brain structures. The cortex also became responsive to strychnine at this time. These electrical reactions could be eliminated by anoxia produced by clamping of the umbilical cord. At this time of appearance of cortical activity there is a diminished reflex response to external stimulation in the animal. The neuromuscular activity exhibited is greater in younger fetuses than in the older. Cortical inhibition, then, is implied in the older animal.[9] The critical development of permeability to sodium[9] correlates with the concept of Hodgkin and Katz that the action potential of nerve may be dependent upon permeability to sodium. Similar studies have been carried on in the developing kitten[10] and rat.[4] Further considerations of the electroencephalogram of the newborn human will be developed below.

REFLEXES AND REACTIONS OF THE NEWBORN (ARBITRARILY, A 14-DAY PERIOD)

The newborn infant is regarded to be the product of a 40-week average gestation and weighing an average of 3500 grams (varying between 2500 and 4500 grams. Arbitrarily, the newborn period to be considered is 14 days. The newborn human is essentially dominated by subcortical brain structures and a detailed analysis of these is not possible utilizing the usual neurological examination as carried on in the adult human. No complete inventory of the total behavior of the newborn has been compiled as yet.

TABLE 1. REFLEXES AND REACTIONS OF THE NEWBORN

Head and face
- Ciliary
- Photomotor
- "Doll's Eye"
- Light orientation, ocular pursuit
- Cardinal Points of Mouth (sucking, rooting)
- Auriculocephalic

Neck
- Tonic reflex (Magnus)
- Head uplifting

Upper extremity
- Moro ("crossed arms")
- Return into flexion
- Grasping

Lower extremity
- Crossed lengthening, adduction
- Grasping
- Straightening
- Automatic walking

Trunk
- Incurvation
- Straightening

Labyrinthine responses
Tonus of neck, trunk, and extremities
Deep reflexes
Superficial reflexes (abdominal, plantar)

However, there have been a number of analyses such as developed by Andre Thomas and Ste. Anne Dargassies,[20] McGraw,[21] and Pieper,[27] which are being incorporated into our neurological evaluation of the newborn. We have made an attempt to apply their methods and to validate the various induced phenomena.

The normal newborn child has responses or reactions mediated by subcortical structures and necessary for the sustaining of life: those concerned with breathing, sucking, swallowing, intestinal peristalsis, micturition, defection and vomiting. In addition, the newborn can cry, sneeze, cough, hiccough, and yawn. Shivering, trembling, breath holding and even "smiling" have been observed in the newborn. Moderate general tremulousness is quite common. The so-called deep tendon reflexes may be elicited from all areas, particularly the biceps and patellar reflexes. The Achilles reflex is

often not present, possibly because of the relaxation of the gastrocnemius muscle and relative hypertonia of the dorsal flexors of the foot. Many of the superficial skin reflexes, such as the abdominal and cremasteric reflexes, may be elicited in the newborn, although there is a very great reflexogenous zone. The palmo-mental reflex is absent. The plantar responses are extensor (Babinski). The superficial abdominal reflexes are very variable but may be elicited in many newborn infants. They have been found in the fetus.[11] The major reflexes and reactions are listed in Table 1. It has been emphasized by Thomas and Ste. Anne Dargassies[20] that most of these reflexes and reactions are automatic responses, and that apparently absent reactions must be searched for several times before absolute absence can be concluded. These responses are characteristic of subcortical functioning and disappear almost entirely after two to four months of life in a normal infant born at term. The visual reactions and the deep and superficial reflexes persist, however.

When the newborn child is placed on his back, the head lies indifferently, being incapable of becoming involved in active spontaneous movements before the 10th day. It should not be permanently inclined to one side. The body has little activity, whereas the extremities are animated with mostly asymmetrical nonadaptive movements, such as elevation of the upper extremities and hand to face contact, especially to the mouth. The lower extremities make alternative movements of extension and flexion. The general attitude of the child is always in flexion, similar to fetal posturing.

The newborn shows many eye reflexes. Lightly stroking the eyelashes causes ipsilateral or bilateral eye closure (the ciliary reflex). A strong light causes blinking (photomotor response), while a mild light produces the pupillary reflex. In the doll's eye phenomenon, elicited in the first 10 days of life, the ocular globes stay fixed and do not follow the head when it is rotated or tilted, or they move in the opposite direction.

By the 10th day postnatally certain infants demonstrate beginning ocular pursuit of moving objects and this is occasionally seen earlier (even in the first day) if bright colored objects are used, such as a ball of bright red wool. There is some difference of opinion concerning the visual function of the newborn.[8] Myelinization is minimal in optic pathways. Certainly the pupils react to light but the amount of visual acuity present is not apparent. Within the first few days of life many infants are able to fixate gaze upon a field of vision or follow a bright object moving across it. Distance accommodation and convergence do not occur until later, and probably definite object vision coincides with these developments. Coordinated eye movements, especially laterally, are mediated by brain stem nuclei, and it should be noted that certain incoordinations may appear transiently later when there is

a transition to cortical controls of conjugate eye movements. The corneal reflex is present. There is a great deal of variation in response to an attempt to make the child blink his eyes by a quick hand movement (threat). This usually appears consistently at the age of several weeks along with accommo-

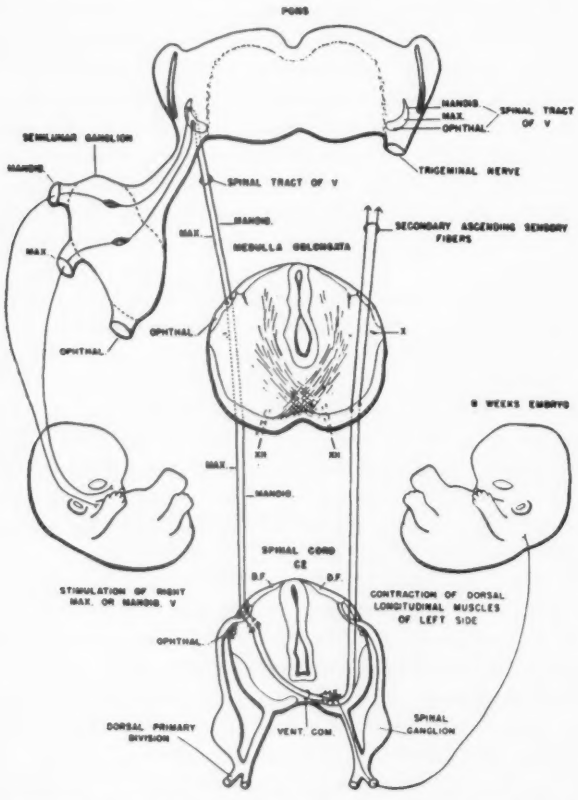

FIG. 1. Diagram of the probable reflex pathway for contralateral neck and upper trunk reflexes associated with facial stimuli, especially in the maxillomandibular trigeminal area, in the early human fetus. (From Fig. 4, T. Humphrey, *J. comp. Neurol.*, 1952, *97*, 180.)

dation responses. The function of the auditory system is also difficult to evaluate. There is little or no significant myelinization in the connections of the acoustic nerve to the cereral cortex or even the thalamus.[8] However, as seen in electroencephalographic studies, evoked responses to both sound and

light stimuli may be elicited in the newborn. The response to sound is generalized and diffuse. One has to separate the effect of vibrations per se from the auditory stimulus.

In the region of the mouth the cardinal points reflexes[20] may be elicited along with sucking and rooting responses. Repeated stimulation of the angles of the mouth, the center of the upper lip and that of the lower lip (cardinal points) causes lip movements towards the stimulating finger, tongue movements in the same direction, followed by head rotation.[20] The neural pathways for these important basic reflexes, concerned with feeding, are already laid down in the early human embryo, even at eight weeks or 22 mm. crown-rump length (Fig. 1).[16] Gustatory responses also may be obtained. These reactions are stronger when the child is hungry. Another cranial sensory response is the auriculocephalic: stimulation of the skin in the region of the ear results in rotation of the head to the opposite side.

Examination of the neck shows that extensor tonus is predominant. A head-uplifting reflex may be elicited by pulling a supine infant upwards into a sitting position.[20] The tonic neck reflexes of Magnus and de Kleijn[23] are inconsistent in almost all examinations of normal newborns in our experience. Classically, with the infant supine, rotation of the head should produce extension or increased extensor tone of the limbs on the side to which the jaw is turned, and flexion of the contralateral (or occiput) limbs. The position of the upper limbs is not consistently maintained in relation to spontaneous or passive movement of the head.

The Moro reflex is a true reflex and one of the best indices of the neurological status of the infant. There are many ways of eliciting this reflex (each producing extension of the head). A simple, effective method is described by Thomas and Ste. Anne Dargassies.[20] The infant is lifted by the arms, without necessarily lifting the head from the supporting surface, and the limbs suddenly released. The phases of the reflex include first, extension and abduction of the arms with wide-open hands and fingers. This is followed by a crossed-arms or embracing appearance. Occasionally the reflex is incomplete, and the second part is produced so that the fingers remain flexed. Also, the thumbs or index fingers may retain the form of a hook. In addition there is extension of the spine and legs. During the first few weeks of life this reaction becomes more pronounced and decreases until finally a simple "body jerk" is seen. It appears to be due to an activation of all motor groups caudal to mid-brain. Asymmetries are often indicative of neurological abnormality.

The reactions of the upper extremity also include a tonus with flexor predominance, and a reflex of return to flexion when the arms are extended passively. The grasp response of the fingers is a tonic reflex of flexors (not

physiologically similar to abnormal grasp in adults) which often may be strong enough to allow a total lifting of the entire infant. Occasionally the triceps reflex is not present since there is often a restrictive hypertonicity of the flexors.

The lower extremities may be tested for tonus by maneuvering the foot towards the corresponding ear. Crossed lengthening and adduction may occur. There may be grasp responses of the toes (plantar grasp) on stimulation of the sole of the foot. The Babinski reflex is often variable in the newborn in the first few days and has a large reflexogenous zone.

With the infant in the vertical position walking movements may be induced automatically, as well as straightening activities of the legs, particularly when the feet are placed flat and the trunk is inclined forwards.[20] A stepping-up response may appear before the 10th day of life but is occasionally not elicited in the newborn. These are essentially tactile placing reactions.

Incurvation reflexes of the trunk[20] are quite constant. These are elicited with the infant in a suspended prone position. The skin is stimulated between the twelfth rib and the iliac crest and the trunk develops a lateral flexion towards the stimulated side. Further postural adjustments may be evaluated by holding the infant in an upright position and rotating, or in an inverted position. Head and eye deviation response may indicate the integrity of the labyrinthine system.[20]

The newborn shows a predominance of flexor muscles at the thigh and knee. The upper extremities become flexed and abducted on the chest. The child then has an active upward and downward movement of the body with some torsion of the trunk muscles. This type of flexor dominance lasts for 4 to 6 weeks when an extensor development takes over control.

When the infant is placed in a ventral or prone position, the lower extremities may be very active and show alternating movements of flexion and contraction producing an almost creeping activity. McGraw[21] showed that when a newborn infant is submerged in water in a prone position, rhythmic associated flexor-extensor movements develop in the upper and lower extremities with trunk flexion similar to swimming motions. In the prone position there is less spontaneous movement in the upper extremities probably related to the development of a degree of cortical inhibitory control over the subcortically mediated activities of these extremities. Also, in the ventral position, a synergistic movement between head turning and arm movements may occur. These reactions can be brought out more clearly if some pressure is produced on the buttocks of the corresponding side. Many of these reflexes and reactions of the newborn may be interpreted in terms of basic labyrinthine righting responses,[22] such as body acting on head and

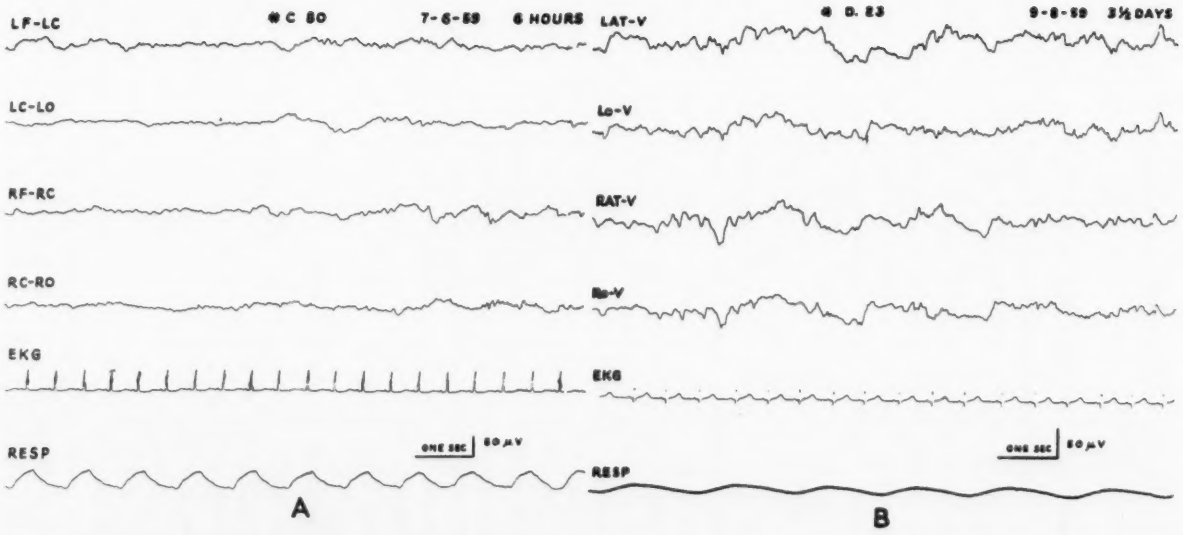

FIG. 2. Electroencephalogram of a normal awake newborn human.

A. Irregular low-amplitude slow wave and some 6-8 cycles per second activity at age of 6 hours.

B. More regular 4-6 cycles per second activity on background rolling ½-1 cycle per second waves at 3½ days.

The labelling of the recordings in this and the following figures is according to the following code of electrode derivations: R = right, L = left, F = frontal, C = central, O = occipital, T = temporal, AT = anterior temporal, V = vertex, PM = posterior midline, M = midline. EKG = electrocardiogram, RESP = respirations, PH. STIM. = photic stimulation.

body acting on body. They probably represent primitive contactual responses with the physical environment.

NEUROLOGICAL SIGNS TO BE CORRELATED WITH A PATHOLOGICAL STATE

The significance of normal variations is still to be determined. However, signs of frank or definite central nervous system disturbance are: Moro reflex absent or incomplete; ocular signs, such as a fixed, staring gaze and nystagmus; a generalized motility disorder, either spontaneous or provoked, such as immobility or exaggerated agitation; abnormal movements such as convulsions or excessive tremors; marked alterations of tonus such as hypertonia or flaccidity, generalized or localized to an extremity or region (asymmetry); phenomena such as persistent hanging of the neck, rigidity of the trunk, or opisthotonus. Sometimes myoclonic-like seizures may be precipitated by tapping the thorax. These signs have been found in 30 per cent of newborns with an oxygen arterial saturation (umbilical vein) below 50 per cent.[23] The pathological signs have been coincident with severe respiratory distress at birth along with cyanosis, gasping, funneling of the chest and respiratory pauses longer than two minutes, severe bradycardia, and definite meconial staining of the amniotic fluid. Persistent asymmetrical and multiple deviant findings are of greatest significance. About 30 per cent of infants with slightly low oxygen saturation at birth (between 50 and 60 per cent) have shown mild abnormalities[23] similar to the above, but less intense. It should be noted that about 10 per cent of children with normal oxygen arterial saturation at birth showed questionable neurological signs indicating involvement of other etiological factors.[24] In a number of instances, mild deviant reactions and reflexes, especially isolated ones, may clear completely and thereafter the infant may develop normally. These require further analysis and follow-up study, however.

THE ELECTROENCEPHALOGRAM OF THE NEWBORN

There have been only a few studies of the electroencephalogram derived directly from the brain of the human fetus.[2, 20, 28] Low voltage fast waves ranging from 10 to 30 cycles per second were found superimposed on irregular low to medium voltage slow rhythm ranging from 1 to 3 cycles per second. In certain prematures at 5½ to 6 months, 4 to 5 cycles per second and 9 to 12 cycles per second low voltage rhythms appear on oscillations of about ½ cycle per second.[6, 7, 12] At 6 months, interhemispheric derivations show intermittent 5 cycles per second waves especially from the frontal region and at 7 to 8 months there are irregular variations, with none of the significant faster waves seen in the younger prematures.[6, 7]

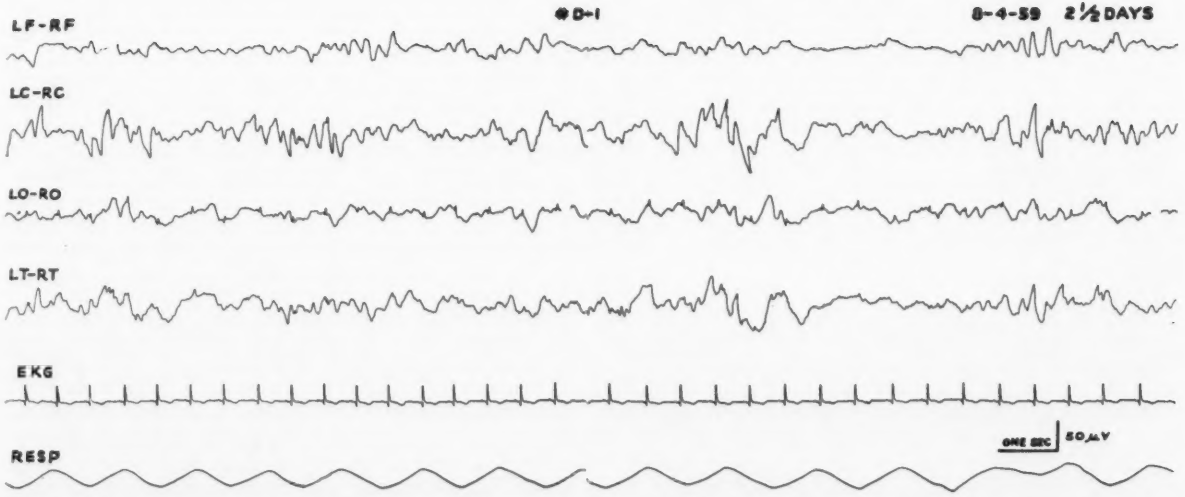

FIG. 3. Electroencephalogram of a normal sleeping newborn human at age 2½ days. Irregular 4-6 cycles per second spindles are present as well as diphasic, high amplitude sharp theta waves, especially from the central and temporal regions bilaterally.

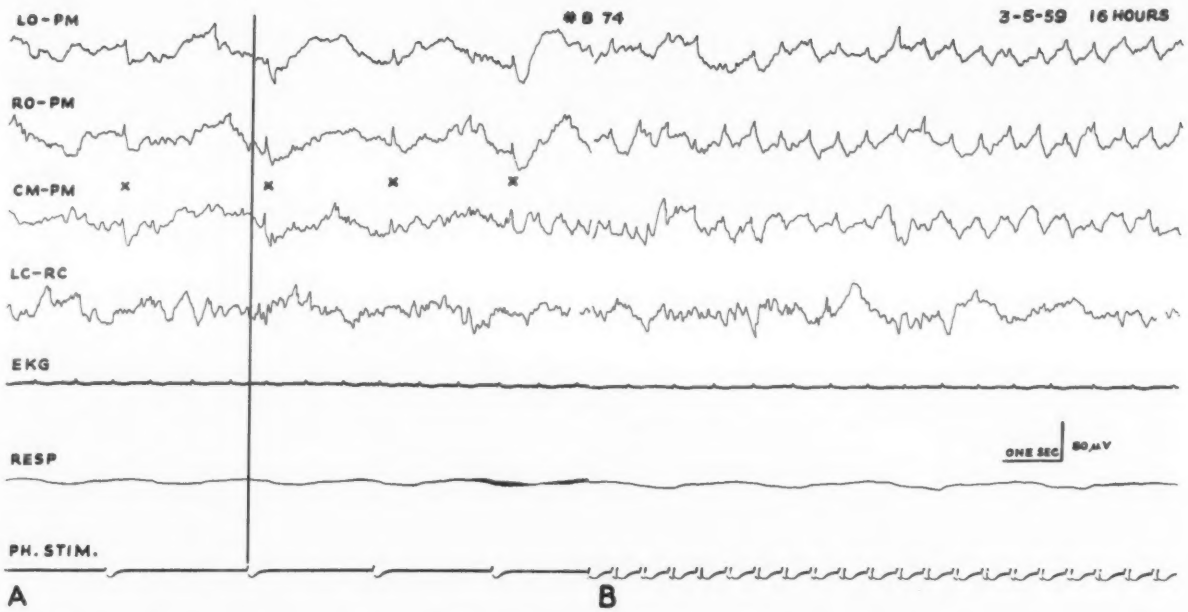

FIG. 4. Evoked electroencephalographic responses to photic stimulation in a newborn human, age 16 hours.
A. Occipital responses, usually diphasic, with amplitudes of 30-50 μv and latency of 200 msec.
B. Photic driving effect. Responses mainly from mid and lateral occipital leads at a stimulus frequency of 3 per second, with paired stimuli.

Previous electroencephalographic studies of the newborn have been reviewed in comparison with our own developing experiences. The electroencephalogram of the newborn human is characterized by continuous, irregular, asymmetric slow waves from all areas[5, 7, 8, 13, 14, 15, 19, 28] (Fig. 2). There is no evidence of steady, organized rhythms although brief rhythmic periods may occur lasting ½ to 4 seconds. The amplitudes range from 5 to 150 microvolts and the frequencies between ½ and 2 cycles per second. Occasionally, medium voltage 3 to 4 cycles per second and low voltage 7 to 9 cycles per second ranges are present. Fast, 20 to 25 cycles per second, activity from the parietal-occipital region of the newborn appears usually for a few days and then disappears only to return later during the first year. The records of newborn infants during the waking and sleeping states are often indistinguishable, but occasionally differentiating rhythms appear depending on the depth of sleep (Fig. 3).[9, 13, 19] Some infants show low voltage 12 to 14 cycles per second spindles from the central region during sleep within a few days after birth. These spindles are poorly defined and of low amplitude but gradually become more characteristic. During drowsiness, irregular 2 to 5 cycles per second slow waves may appear, becoming better modulated with regard to frequency and amplitude as the child becomes older. Occasionally, the waves in this frequency range assume spindle form during sleep, often alternating with intermittent flattening (Fig. 3).

Some investigators have indicated that arousal patterns are not well defined and do not generally appear in the newborn.[18] Yet, they clearly may be elicited.[6, 8] Reactive arousal consists mainly of diphasic slow waves followed by rapid oscillations of about 8 to 14 cycles per second appearing mainly from vertex electrodes but also from other areas in lower amplitudes. These transient responses to sensory stimulation have been called K complexes. They should be differentiated from central sharp wave transients appearing usually by the age of 5 or 6 months. The Moro reflex tends to disappear at about the time the cerebral cortex responds consistently to these reactions. A more common arousal response in the newborn electroencephalogram is a flattening, especially during sleep.[6, 8] During the waking state or sleep, a loud sound may produce, 2 or 3 seconds later, a flattening of the electroencephalogram which may last for 7 to 8 seconds. Flattening responses may be preceded by a burst resembling a K complex or a single sharp theta wave. Less commonly they occur to visual stimulation. Definite sharp wave responses, of 0.1 to 0.3 second duration, to visual stimulation have been obtained both with ON and OFF reactions, as in the work of Ellingson[8] (Fig. 4A). There is a longer latency than in adults, between 150 and 220 milliseconds (adults average 50 to 60 milliseconds). Photic driving has been a rare and striking response (Fig. 4B), once thought to be un-

obtainable. Much work has to be done with reactions during the waking and sleeping states, especially with autonomic correlates, such as respiration and heart rate, in order to clarify the normal variations.

Correlations between the electroencephalogram and clinical status in the stressed newborn are illustrated by two brief case presentations. The first case is that of a child developing respiratory difficulty after birth along

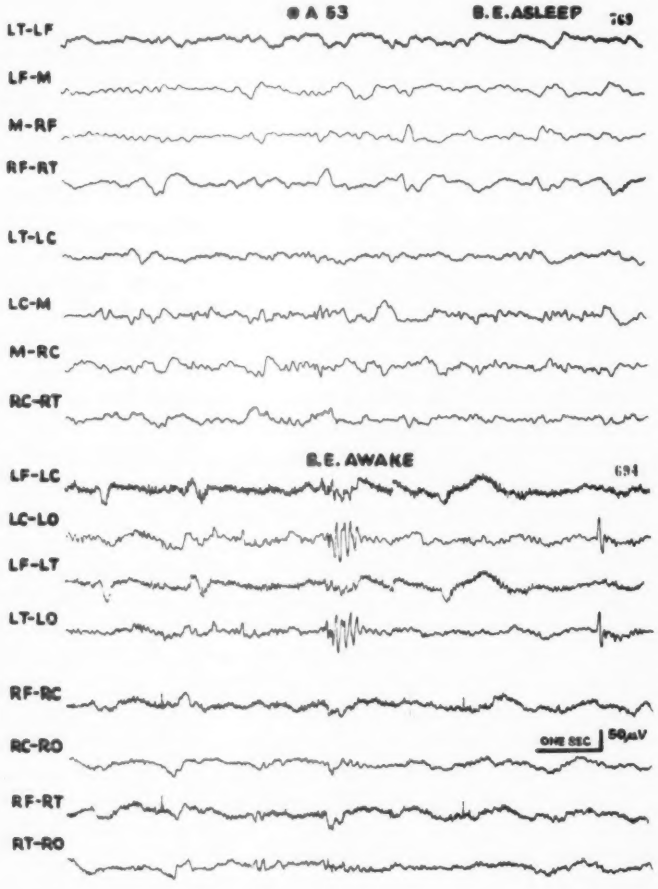

FIG. 5. Abnormal electroencephalogram of a three-day-old stressed infant who developed a seizure. The recording shows bursts of sharp waves and isolated spiking of up to 100 μv amplitude from the left occipital region during the waking state.

with an absent Moro response and weak grasping and sucking reflexes. The electroencephalogram in the third day (Fig. 5) showed bursts of sharp waves from the left occipital region along with spike activity from that same area. The day following the electroencephalogram, the child had a generalized convulsion. The second case is of an infant who was born with the umbilical cord around his neck. The child did well for 4 days but then

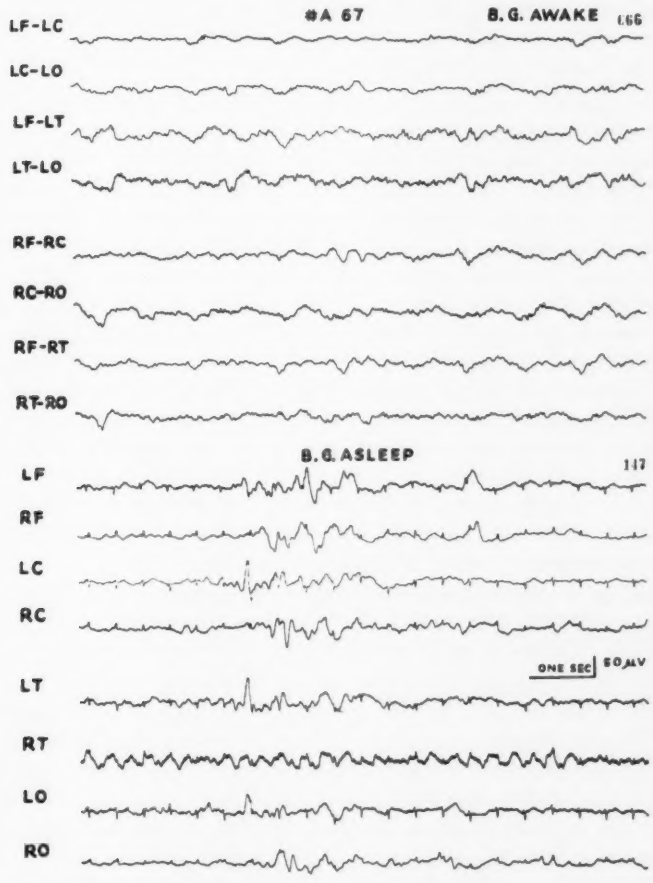

FIG. 6. Abnormal electroencephalogram of a four-day-old stressed infant with a seizure disorder. The electroencephalogram shows a left temporal sharp wave or slow spike focus during sleep. The recording during sleep is with monopolar technique utilizing ipsilateral ear electrodes as reference.

began to have generalized seizures. The neurological examination showed generally decreased muscle tone, lack of light following, inequality of the pupils without light reaction, and no attempt at maintaining flexor tonus. The Moro reflex was absent. The sucking response was slight on the right and not present on the left. The electroencephalogram (Fig. 6) showed a left temporal spike focus during sleep. In both these instances, therefore, the development of a seizure state was associated with spike discharges indicating an epileptogenic focus in the electroencephalogram.

COMMENTARY AND CONCLUSIONS

A comparison summary of the early maturation of the electroencephalogram and cerebral reactivity along with early neurological and psychomotor maturation is shown in Table 2. The electroencephalogram of the newborn is undifferentiated, irregular and variable. Reactivity to stimuli (awake or asleep) is that of general flattening, diffuse irregular discharge, and occasionally sharp primary responses with increased amplitude, often followed by flattening. The newborn shows archaic reflexes dominated by subcortical mechanisms also producing the Moro, automatic walking, creeping, static straightening and grasping responses. Labyrinthine phenomena are prominent. The tonus of the head is little controlled. There is some light perception but no definite control of ocular movements. Responses to auditory stimuli are generalized and usually result in a Moro reflex. These phenomena persist for 2 to 3 months after which time the electroencephalogram becomes better organized, particularly with the primary responses to photic stimulation, along with more frequent diffuse sharp waves during sleep. The child has better control of tonus of his head and ocular motor coordination. He responds to auditory stimuli by an arrest of movements.

A lack of or slow cortical development might result in the persistence of archaic subcortical reflexes and reactions. This persistence would be due to the lack of development of so-called cortical dominance over, or "inhibition" of, subcortical reflexes or reactions. Lesions of the subcortex, particularly the upper and middle brain stems, diencephalon and mesencephalon might produce abnormalities in the subcortical reflexes themselves, and in tonus of the neck, trunk and extremities. Unilateral disturbances would be manifest by distinct asymmetries. It will be important to attempt to correlate a later development of motor disturbances such as paralysis, spasticity, hypertonus or rigidity, and the various dyskinetic states (athetosis and dystonia) with neuromuscular phenomena observed in the neonatal period.

Abnormalities in the infant's electroencephalogram are seen mainly as seizure discharges, in particular, spikes and sharp waves, especially per-

TABLE 2. MATURATION OF THE EEG AND CEREBRAL ACTIVITY
(Modified from Dreyfus-Brisac and Blanc[8])

ELECTROENCEPHALOGRAM	*Birth*	*3 months*	*5 months*	
Topography	Undifferentiated	1. Topographical organization of the EEG		Occipital activity: rhythmic 5-6 cps
Occipital activity	Sl. Response to eye opening Responses to photic stimulation	2. Occipital 3-4 cps 3. Responses to photic stimulation		+
Reactivity during sleep	1. General flattening responses 2. Diffuse, irregular discharges 3. Diphasic responses, increased amplitude, then flattening	4. Diffuse sharp waves		Progressive differentiation
NEUROLOGICAL—PSYCHOMOTOR MATURATION				
Archaic reflexes	Moro Automatic walking Creeping Static straightening Grasping			
Motor tonus		Control of tonus of the head	Voluntary prehension	Sitting position
Vision	Light perception	Oculomotor coordination Sweeping of space	Macular vision	
Hearing	Generalized Reactions Moro	Arrest of movements	Mimicry responses	Rotation of head
Speech	Cooing sounds	Murmuring		Repetition of syllables

sistent focally, and as lack of reactivity previously present. Gross asymmetry of flattening, and delta (½-3 cycles per second) activity (particularly with phase reversals) would be suggestive of focal structural lesions. The appearance of definite spike discharges may indicate the development of a clinical seizure state, but not always, since these discharges may only represent a potentiality. The persistence of newborn or other early patterns as the child develops may be correlated with other slowly developing cerebral functions, perhaps with psychomotor retardation in a general sense.

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ROBERT P. DAVIS*
WILLIAM B. BLYTHE**
MARGARET NEWTON†
LOUIS G. WELT‡

Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina

THE TREATMENT OF INTOXICATION WITH ETHYNYL-CYCLOHEXYL CARBAMATE (VALMID®) BY EXTRACORPOREAL HEMODIALYSIS: A CASE REPORT

Since the introduction of extracorporeal hemodialysis for the management of renal failure, its usefulness in the treatment of otherwise fatal poisoning by various chemical agents has been repeatedly demonstrated. Among these agents have been various barbiturates,[3] salicylates,[4] and bromide.[7] Recent experience with a case of intoxication with ethynyl-cyclohexyl carbamate (Fig. 1), a short-acting nonbarbiturate hypnotic,[5] provided an opportunity to demonstrate its dialyzability. Although the poisoning proved fatal in this instance, the ability to remove an appreciable quantity of the drug by hemodialysis suggests that patients with severe intoxication coming under observation earlier may be treated by this method more successfully.

CASE HISTORY

M.F.K., NCMH Unit No. 05-26-69

A 24-year-old single white female graduate student was brought to the Emergency Ward of the North Carolina Memorial Hospital at 9:30 p.m. on 9/25/58. She had been found comatose in her apartment shortly before with the beginning of a "suicide note" and an empty prescription bottle discovered near her body. The prescription had been refilled one week previously after a long interval for at least thirty 0.5 gram tablets of ethynyl-cyclohexyl-carbamate (Valmid®, Lilly). The patient was last heard from specifically 26 hours prior to the discovery prompted by her having missed several specific appointments throughout the day. Past medical history, obtained from friends and previous medical record, was noncontributory. There was no personal history of diabetes, epilepsy, trauma, syncope, cardiac, pulmonary or renal disease. Family history was also noncontributory.

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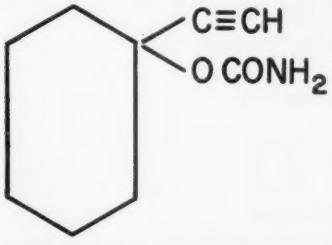
* Formerly Assistant Professor of Medicine, University of North Carolina School of Medicine. Present address: Department of Medicine, Albert Einstein College of Medicine, Yeshiva University, Eastchester Road and Morris Park Avenue, New York 61, New York.
** Fellow, Life Insurance Medical Research Fund.
† Fellow of the National Foundation.
‡ Professor of Medicine.
Received for publication October 21, 1959.

Physical examination showed a well-developed, well-nourished white female, comatose and cyanotic. There was no evidence of vomiting. Respirations were shallow at 24/minute. The blood pressure and pulse were unobtainable. Temperature was 95.4° F., p.r. Hydration was fair. External examination revealed a 6 x 6 inch pressure point over the right hip, suggesting that the patient had lain on that side for a long period. There was no evidence of trauma to the head or the rest of the body, nor was there sign of fracture. The pupils were normal in size with the left pupil slightly larger than the right; there was no pupillary response to light. Ear, nose, and throat were normal. The neck was supple and free of venous distention. There were numerous rhonchi heard bilaterally in the chest; these were cleared considerably on suction. The heart was normal in size and showed a normal sinus rhythm at a rate of 78. The aortic and pulmonary second heart sounds were equal in intensity and there were no murmurs. The abdomen was soft with normal bowel sounds audible. No masses or organs were palpable. Neurological examination showed coma, areflexia, generalized flaccidity, complete unresponsiveness to painful stimuli, and no spontaneous movement. Plantar response was normal bilaterally.



1- ethynyl - cyclohexyl carbamate

ETHINAMATE

FIG. 1. Structural formula of ethinamate.

Laboratory data indicated an hematocrit of 60 per cent and a white blood cell count of 7875 cells/cu. mm. The sedimentation rate and differential cell count were normal. Urinalysis showed a cloudy, amber urine, pH. 4.5, specific gravity 1.018, no protein or acetone, 2+ sugar. Except for many epithelial cells, the urinary sediment was clear. There was no gross or occult blood in the stool.

On arrival at the hospital, an endotracheal tube was inserted and oxygen therapy begun with clearing of the cyanosis but no change in neurological status. An infusion of l-norepinephrine was also started at once with a rise in blood pressure to 90/60 and a return of palpable, symmetrical peripheral pulses. A search of the literature and consultation with the manufacturer and with several poison centers throughout the country revealed no specific therapy or antidote.

Laboratory data shortly after entry revealed a blood CO_2 content of 20 mEq./L. and a blood sugar of 368 mg.%. The blood sugar rose over the next twelve hours to 832 mg.% and then fell to 444 mg.% prior to the onset of hemodialysis. The hyperglycemia was concomitant with massive l-norepinephrine infusions. The blood and urine remained free of acetone throughout, and the patient did not appear to be in diabetic coma. The blood sugar fell to 144 mg.% on hemodialysis. Urine sugar fluctuated between 2+ and 4+ on catheterized specimens. During the initial twelve hours the urine output dwindled as the patient developed 3+ albuminuria, cylindruria, and microscopic hematuria and pyuria. Specific gravity remained at 1.018 and pH at 4.5.

Despite continuous support by vasopressor agents, oxygen, endotracheal suction, bronchoscopy for left lower lobe atalectasis of the lung, antibiotics because of x-ray evidence of pneumonitis, gastric suction because of coffee-ground vomitus, and the

administration at various times of dextrose in water, hypertonic and isotonic saline and plasma, the patient continued to show clinical and chemical evidence of deterioration. It became necessary to maintain respiration with a Bennett respirator; the need for vasopressor agents for the maintenance of detectable blood pressure increased and with it the need to administer excessive volumes of fluid in the face of diminishing urine output and the suspected development of acute renal failure. The blood urea nitrogen was normal, but the acidosis worsened over the initial 12 hours of hospitalization; the CO_2 content fell to 9.5 mEq./L.; other chemical values were sodium 115 mEq./L. at the time the blood sugar was 386 mg.%, potassium 3.0 mEq./L., chloride 93 mEq./L., total protein 4.1 gr.%, phosphorus 7.7 mg.%. Arterial blood pH was 6.88, pCO_2 43 mm. Hg and bicarbonate 9.3 mEq./L., representative of a mixed metabolic and respiratory acidosis. Electrocardiogram showed slight prolongation of the QT interval with a sinus rhythm at a rate of 79/minute.

In the hope that ethinamate would prove dialyzable and in the face of the continued moribund state of the patient, hemodialysis was begun 18 hours after entry by means of a disposable coil artificial kidney (Travenol Laboratories, Inc., Morton Grove, Illinois). After six hours of hemodialysis, there was no evidence of clinical or chemical improvement. Hydrocortisone was administered without noticeable salutory effect. Arterial blood showed a pH of 6.65, CO_2 content 8.1 mEq./L., sodium 133 mEq./L., and potassium 4.8 mEq./L. The hematocrit had fallen to 45. Because of the demonstration of an acetylenic compound in an ether extract of the dialysate on qualitative test with alkaline ammoniacal silver solution (a control test with commercial ethinamate was also positive), it was decided to continue the dialysis for another six hours. At the end of this period the arterial blood CO_2 content had risen to 10.1 without significant change in other chemical studies, except for the aforementioned fall in blood sugar to 144 mg.%. At this point, after 12 hours of hemodialysis, the patient developed pulmonary edema and expired. Post-mortem examination showed pneumonia, multiple pulmonary emboli with infarction, hepatic and splenic congestion, and bilateral cortical necrosis of the kidneys.

DISCUSSION

Ethynyl-cyclohexyl carbamate (ethinamate, Valmid[R] Lilly) is a short-acting nonbarbiturate hypnotic drug with a short duration of action.[3, 4, 5, 9] The therapeutic dose is considered to be very much less than the toxic dose, but little has been done to elucidate its pharmacology. One patient is reported to have taken 28 gm. of the medication without fatal outcome.[1] No antidote is known. The kidney plays no role in the metabolic transformation of ethinamate while data on the role of the liver are contradictory.[5, 7]

The metabolic fate of ethinamate in rats has recently been clarified by McMahon.[6] Seventy-three per cent of a 50 mg./Kg. intraperitoneal dose (labeled with C-14 on the carbonyl group) was eliminated within eight hours, 10 per cent as respiratory CO_2 and 63 per cent in the urine as unchanged ethinamate and some metabolite of the drug. The metabolite was identified by paper chromatography and subjection to the action of β-glucuronidase as mainly hydroxy-ethinamate and its β-glucuronide in

approximately equal amounts. Of the urinary excretory products, 2 per cent was unchanged ethinamate, 89 per cent hydroxy-ethinamate and 9 per cent unidentified metabolites. The acetylenic group remained unchanged by the body. Whether hydroxy-ethinamate has any hypnotic effect has not been reported.

There are many unexplained features in the course of the patient reported above. The rapid onset of a very severe acidosis without ketosis and clinically not resembling diabetic acidosis despite the elevated blood sugar (possibly attributable to norepinephrine administration) remains unexplained. A test of a normal urine specimen to which a small amount of ethinamate had been added showed only a trace reaction to Clinitest[R] tablet and a negative reaction to glucose oxidase impregnated urinary test paper, suggesting that the ethinamate alone could not account for the elevated sugar. While the hyponatremia could be explained on the basis of the elevated blood sugar, the marked elevation of the hematocrit remains mysterious in the face of the absence of evidence of significant dehydration. Possible shifts of fluid internally out of the plasma may account for this, but the stimulus and mechanism for this shift are unrecognized here.

Hemodialysis was undertaken because of the lack of progress of the patient already moribund and in cardiovascular collapse, in the hope that the drug would prove dialyzable. The dialysates from the two six-hour runs on the artificial kidney were very kindly analysed by Dr. John S. Welles (The Lilly Research Laboratories, Eli Lilly and Co., Indianapolis, Indiana) by a chromatographic technique. The total amount of ethinamate and hydroxy-ethinamate removed is indicated in Table 1:

TABLE 1.

	Ethinamate	*Hydroxyethinamate*
Dialysate No. 1	345 mg.	190 mg.
Dialysate No. 2	460 mg.	240 mg.
Total	805 mg.	430 mg.

Although only 1.23 gm. of ethinamate are accounted for on the two dialyses, hemodialysis was not begun until an estimated 40-44 hours following the ingestion of the medication, whose action and stay in the body are known to be short. The amount removed may, in this light, be significant. For this reason, then, the demonstration of the dialyzability of ethinamate and its metabolic product appeared worthy of a report in the hope that cases of severe intoxication appearing earlier in their course may have a more favorable outcome. The appearance of a quantity of the drug in the second

six-hour dialysate equal to the amount in the first dialysate may not be a reflection of poor dialyzability from the blood but may, rather, indicate an intracellular location across a membrane of limited permeability to the drug. The effect of the patient's extreme mixed metabolic and respiratory acidosis on this permeability is conjectural. In the absence of plasma level determinations, the gradient and effect of protein binding cannot be evaluated. The need for prolonged or repeated hemodialysis in cases of ethinamate intoxication should therefore be anticipated.

SUMMARY

A fatal case of ethinamate intoxication is reported. The patient was treated by hemodialysis unsuccessfully, but the demonstration of significant amounts of ethinamate and its metabolic product in the dialysate warrants an early trial of this mode of therapy in other severe cases of ethinamate intoxication unresponsive to other measures.

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OLE STORSTEIN*
MASSIMO CALABRESI**
ROBERT G. NIMS†
FRANK D. GRAY, JR.‡

Cardiopulmonary Laboratory, Department of Internal Medicine, Yale University School of Medicine, and The Veterans Administration Hospital, West Haven, Connecticut

THE EFFECT OF HISTAMINE ON THE PULMONARY CIRCULATION IN MAN¶

The influence of intra-alveolar pressure and respiratory mechanics on pulmonary hemodynamics has been extensively studied.[4] Rodbard has presented the view that bronchomotor tone is a prominent factor in the regulation of pulmonary blood flow,[23] but the effect of bronchoconstriction on pulmonary pressure and flow has, so far, been studied very little in humans.[26] If the pulmonary hypertension observed in patients with broncho-obstructive disease is to be ascribed, even in part, to the obstruction itself, then one should be able to influence cardiac output or pulmonary vascular resistance by administering agents known to produce bronchospasm.

The present study was designed to demonstrate the effect of histamine on pulmonary hemodynamics in a group of hospital patients with chronic bronchitis, pulmonary emphysema, or other lung diseases associated with impaired ventilation. It was hoped that the drug would produce in these patients a disproportionate bronchoconstriction even in doses having only slight primary circulatory effect. Effects ranging from no bronchoconstriction to severe bronchoconstriction were anticipated, however, because of individual variation in homeostatic reflexes and bronchial musculature sensitivity to histamine. The observations presented here describe the circulatory and ventilatory changes produced by small doses of histamine in patients selected on the basis of having chronic pulmonary disease.

MATERIAL AND METHODS

Twenty-one ambulatory, male hospital patients with chronic pulmonary disease were studied. Spirometry and cardiac catheterization were performed on consecutive days

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* James Hudson Brown Memorial Fellow in Medicine. Present address: Sergenfrigt 19, Oslo, Norway.
** Associate Clinical Professor of Medicine.
† Assistant Clinical Professor of Medicine.
‡ Associate Professor of Medicine.
¶ This investigation was supported in part by research grants H1516 C3, C4, and H1952 C2 from the National Heart Institute, Public Health Service, and in part by a research grant from the Fluid Research Fund, Yale University School of Medicine.
Received for publication October 21, 1959.

before and after the subcutaneous injection of 0.6 to 0.8 mg. of histamine phosphate. All subjects had performed the ventilatory tests previously and were thus familiar with the procedures.

On the first day, vital capacity and maximum breathing capacity were measured with the patient supine on a bed gatched 30 degrees from the horizontal, and blood pressure was measured. After a satisfactory baseline record had been obtained, the histamine

TABLE 1. CLINICAL DATA

Patient	*Age*	*Diagnosis*	*Body surface area Sq.M.*	*Dose of histamine phosphate mgm.*
M. M.	39	Tuberculous pleurisy	1.81	0.75
G. L.	69	Pulmonary emphysema, bronchiectasis	1.81	0.80
H. D.	55	Pulmonary emphysema, chronic bronchitis	2.32	0.80
G. G.	69	Pulmonary emphysema, bronchiectasis	1.56	0.70
F. B.	63	Chronic bronchitis, polycythemia	2.17	0.80
D. B.	56	Pulmonary emphysema, chronic bronchitis	1.79	0.60
T. A.	62	Pulmonary emphysema, chronic bronchitis	1.73	0.60
J. M.	62	Mitral stenosis and insufficiency	1.82	0.60
H. W.	56	Chronic bronchitis, liver cirrhosis	1.86	0.60
P. R.	37	Pulmonary tuberculosis	1.68	0.80
W. P.	51	Pulmonary emphysema, chronic bronchitis	1.88	0.70
P. Z.	51	Pulmonary tuberculosis	1.38	0.70
W. M.	32	Chronic bronchitis	1.86	0.80
D. C.	65	Chronic bronchitis, cor pulmonale	1.60	0.60
A. L.	60	Pulmonary emphysema, bronchiectasis	1.55	0.60
G. F.	39	Bronchiectasis	1.80	0.60
F. S.	32	Pulmonary tuberculosis	1.76	0.70
F. F.	60	Pulmonary emphysema, bronchiectasis	1.78	0.70
N. M.	64	Pulmonary emphysema, bronchiectasis	1.98	0.70
P. S.	37	Pulmonary emphysema, chronic bronchitis	1.79	0.70
E. U.	59	Pulmonary emphysema	1.60	0.70
H. A.	45	Pulmonary emphysema, bronchiectasis	1.66	0.70

was injected. Blood pressure was then measured every minute for 15 minutes. Vital capacity and maximal breathing capacity were measured at 3, 7, and 11 minutes. On the following morning cardiac catheterization was performed by standard methods. Cardiac output was estimated by the direct Fick method. Following baseline measurements, histamine in the same dose as that used on the previous day was injected subcutaneously. Pulmonary artery pressures were then recorded every minute, and at the time of maximum histamine effect, as observed during the spirometric studies the previous day, a wedge pressure was recorded. Immediately after, cardiac output was again estimated by the Fick method. Recording of pulmonary artery pressure continued at minute intervals until 15 minutes after the injection. The method of Pederson and Husby was used to establish the zero reference level for the pulmonary pressures.[30]

A five-minute sample of expired air (while the subject breathed room air) was obtained simultaneously with the slow withdrawal of blood samples from the femoral and proximal pulmonary arteries. The expired air was analyzed by the Scholander microanalysis technique, and the blood samples by the Roughton-Scholander method. Arterial carbon dioxide content was measured, using the Kopp-Natelson microgasometer, and arterial pH estimated at body temperature by means of a water-jacketed glass electrode and a Cambridge Research Model pH Meter. The carbon dioxide tension was determined from the Singer Hastings nomogram. Alveolar oxygen tension was calculated using the alveolar air equation, arterial oxygen tension read from the oxygen dissociation curve, and the alveolar-arterial oxygen tension gradient calculated from these data.

RESULTS

Tables 2 to 4 show the observed effects of histamine on vital capacity, maximal breathing capacity, minute breathing volume, alveolar ventilation, heart rate, systemic, pulmonary artery, and pulmonary wedge pressures, cardiac output (expressed as cardiac index), total systemic and pulmonary arterial resistances, arterial oxygen saturation, arterial oxygen tension, alveolar-arterial oxygen tension gradient, and respiratory fluctuations in pulmonary artery systolic and diastolic pressures.

Evaluation of the results showed a statistically significant fall in vital capacity and maximal breathing capacity. The minute volume of ventilation increased in most cases. The alveolar ventilation did not, however, show any significant change in those cases in which it was measured.

The heart rate showed a significant increase, the systemic blood pressure, a fall. The fall in pulmonary artery pressure was also significant, while there was no significant change in pulmonary wedge pressure. Since the average increase in cardiac index from 4.11 to 4.45 liters per minute was not statistically significant, calculated systemic and pulmonary resistance dropped. There was a statistically significant increase both in systolic and diastolic pulmonary artery pressure respiratory fluctuations.

The blood gas studies showed a significant fall in arterial oxygen saturation, no changes in arterial carbon dioxide tension, and a significant increase in the alveolar-arterial oxygen tension gradient. No significant changes in oxygen capacity were noted. In nearly all patients a slight facial flush was observed after histamine, and about one-half of the patients experienced a mild headache.

DISCUSSION

1. *Ventilation*

Histamine in nontoxic doses has no effect on the mechanics of breathing in the normal subject. In patients with asthma or some types of chronic lung

TABLE 2. RESPIRATORY FUNCTION DATA

	V.C. ml.		*M.B.C.* L/min.		$\dot{V}_E$ L/min.		$\dot{V}_A$ L/min.		Sa_{O_2} %		Pa_{CO_2} mm.Hg		*A-a* mm.Hg	
Pt.	*B*	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*	*A*
M.M.	3550	2050	112	65	10.1	12.1	..	..	88	86	..	..	..	..
G.L.	2015	1660	24	17	6.7	9.0	..	..	81	78	..	..	..	..
H.D.	1900	1595	29	22	9.2	11.8	..	..	90	87	..	..	..	..
G.G.	1210	670	9	7	8.2	7.4	..	..	84	71	..	..	..	..
F.B.	2150	1890	39	35	7.6	10.8	4.7	5.5	81	78	45	49	40	44
D.B.	1505	1415	27	17	8.6	12.4	3.8	5.7	95	93	43	38	18	30
T.A.	1825	1470	22	17	11.2	8.7	6.3	5.7	98	96	42	37	5	20
J.M.	2525	1905	41	34	8.6	9.5	5.5	5.1	99	96	35	37	3	12
H.W.	1500	1100	36	19	7.8	7.8	3.2	3.4	87	80	40	36	42	59
P.R.	2670	2500	44	37	7.8	7.8	6.2	6.2	96	92	34	33	25	46
W.P.	2180	2000	54	46	5.7	6.1	4.4	4.9	92	90	35	34	34	46
P.Z.	3520	3520	73	73	7.2	8.9	..	..	83	87	..	..	..	..
W.M.	2420	2640	59	45	8.4	12.4	..	..	92	96	..	..	..	..
D.C.	1290	1160	17	15	8.5	7.3	..	..	86	75	..	..	..	..
A.L.	1095	1050	7	9	6.3	8.3	..	..	88	90	..	..	..	..
G.F.	1500	1410	56	61	13.3	14.5	..	..	88	80	..	..	..	..
F.S.	1425	1425	52	59	6.5	9.9	..	..	87	75	..	..	..	..
F.F.	1320	1630	27	27	6.0	6.7	..	..	87	80	..	..	..	..
N.M.	2700	2740	34	22	7.6	7.7	3.9	3.6	88	83	41	38	41	51
P.S.	2890	2930	83	78	7.7	7.7	5.4	5.1	97	88	36	37	11	45
E.U.	2270	2360	49	27	7.7	7.7	4.1	3.9	92	89	45	45	26	32
H.A.	....	....	..	..	14.4	16.8	..	..	97	93	..	..	..	..
Means	2070	1863	42.57	34.86	8.41	9.60	4.75	4.91	80.82	85.59	39.6	38.4	24.5	38.5
Diff	207		7.36		1.19		0.16		4.3		1.2		14.05	
t	2.45		3.12		3.79		0.65		4.58		1.25		2.6	
	0.025>P>0.010		0.005>P >0.001		0.005>P >0.001		P>0.50		P<0.001		0.400>P >0.200		0.050>P>0.025	

Symbols based on report in *Fed. Proc.*, 1950, *9*, 602.

disease, however, it has a powerful bronchomotor action; the systemic effects of the drug in these patients are similar to those in the normal subject.[6, 29, 33] A fall in vital capacity after histamine has been found in studies of asthmatic individuals.[6, 7, 25] An increase in respiratory minute volume,[1, 33] a decrease in lung compliance,[19] and an increase in airway resistance[18] have been observed in patients with chronic pulmonary disease. Our data agree with these observations. It should be noted, however, that in some of our patients the vital capacity did not fall more than 100 ml. or even increased after histamine; in only nine cases did the vital capacity decrease more than 10 per cent. Furthermore, maximal breathing capacity did not decrease in all of our patients. Alveolar ventilation did not show statistically significant changes in those cases in which it was calculated. A variable effect of histamine on ventilatory function, according to the severity of disease, has been observed by others.[7] The bronchoconstrictor effect of histamine in the dosage used was not demonstrated in all of our patients. Our purpose, however, was to use relatively small amounts of the drug in order to limit its systemic effect.

There are reflexes which serve to maintain a steady state when bronchoconstriction occurs. Most notable are the presso-receptors of the lung which react to increased expiratory pressure by increasing inspiratory effort and the resting volume of the lung. This passively dilates the constricted bronchi; thus, in the intact human subject, bronchospasm may be elusive.

Since bronchoconstriction occurred in some of the patients and not in others, any consistent circulatory change must be unrelated to the bronchoconstricting effect of histamine.

2. *Systemic circulation*

The observed effects on the systemic circulation are in agreement with earlier investigations in man. Weiss, Robb, and Ellis,[33] Wakim, Peters, Terrier, and Horton,[31] and Peters and Horton[21] found an increase in heart rate on the intravenous infusion of histamine, while a fall in systemic blood pressure was observed by Wilber and Brust.[34] Roth and Kvale[24] gave a single intravenous dose of 0.025-0.05 mgm. of histamine base and observed a slight rise after an initial drop in blood pressure. An increase in cardiac output following histamine was observed by Weiss *et al.*,[33] while Wakim *et al.*[31] found an increase in blood flow in all four extremities, as demonstrated by venous occlusion plethysmography. The rise in cardiac output observed in our studies was not statistically significant. This variable effect of the drug may be due to a difference in dose. In the dog under general anesthesia, small doses induce capillary dilatation and an increase in blood flow; larger doses, by further dilatation of the capillaries and small veins, produce a pooling of

TABLE 3. PRESSURE DATA

Pt.	Systemic pressure mm.Hg				Pulmonary artery pressure mm.Hg				Pulmonary artery respiratory pressure fluctuation mm.Hg				"Wedge" pressure mm.Hg	
	B		A		B		A		S		D			
	S/D	M	S/D	M	S/D	M	S/D	M	B	A	B	A	B	A
M.M.	135/90	105	115/70	85	25/15	18	26/13	17	6	7	5	7	..	..
G.L.	100/68	78	90/65	73	31/12	18	25/12	15	5	10	4	12	6	6
H.D.	132/94	107	124/100	108	25/15	20	22/13	18	17	19	15	18	..	..
G.G.	110/70	83	100/65	75	20/8	17	19/8	17	13	13	8	10	3	3
F.B.	95/55	65	105/55	67	26/9	15	20/7	15	18	27	23	32	3.5	3
D.B.	103/87	93	99/72	90	25/11	16	22/9	13	14	16	16	18	4	3.5
T.A.	158/70	108	126/60	89	23/0	9	18/0	6	11	16	9	15	1.5	0.5
J.M.	94/44	56	94/44	56	25/11	18	25/11	18	10	10	5	7	..	..
H.W.	109/72	85	100/67	80	21/12	15	19/10	13	14	21	14	18	6	7
P.R.	140/80	102	106/60	78	35/12	20	18/7	11	5	8	6	9	5	5.5
W.P.	126/88	100	122/71	92	23/12	16	21/11	15	10	10	12	12	5.5	6
P.Z.	120/70	83	75/50	58	12/7	9	10/4	6.5	2	2.5	2	2.5	2	1.5
W.M.	117/86	96	106/92	96	27/11	16	25/12	16	7	13	5	13	..	..
D.C.	120/73	90	90/57	78	62/24	35	45/12	25	25	22	8	12	..	..
A.L.	105/70	85	80/55	63	22/5	11	17/6	9	9	13	6	10	3	3
G.F.	100/55	70	80/50	60	15/5	10	15/6	10	13	16	12	15	3	3
F.S.	115/85	100	.....	..	24/12	16	21/7	13	10	17	12	17	..	..
F.F.	130/70	95	115/60	80	19/11	13	19/11	13	6	8	6	8	2	2
N.M.	100/56	75	81/50	60	.....	..	.....	...	5*	10*	5*	10*	..	..
P.S.	94/58	74	78/60	66	23/10	15	16/5	11	5	10	5	11	8.5	6
E.U.	120/66	90	102/66	84	17/3	9	17/4	9	5	10	5	8	4	1.5
Means		87		76.9		15.8		13.3	10	13.26	8.71	12.6	4.3	3.8
Diff			10.1				2.8			3.24		3.86		0.55
t			5.29				2.8			4.7		7.28		1.45
			P<0.001				0.025>P>0.010			P<0.001		P<0.001		0.200>P>0.100

(Patient H.A. is not included in this Table because insufficient data were obtained.)

* = Right atrium
B = Before
A = After
S = Systolic
D = Diastolic

blood in the periphery, with reduction of the venous return and of the cardiac output.[27] However, independent of the doses used, the circulatory effects of histamine vary greatly in different species according to the method of administration and the organs primarily affected.

TABLE 4. RATE, FLOW, AND RESISTANCE DATA

	Heart rate		*Systemic blood flow L/min/M²*		*Total peripheral resistance dynes-sec.-cm.⁵*		*Pulmonary artery resistance dynes-sec.-cm.⁵*	
Patient	*B*	*A*	*B*	*A*	*B*	*A*	*B*	*A*
M.M.	88	94	6.1	5.1	756	740	...	...
G.L.	63	80	3.4	3.7	1200	1070	184	124
H.D.	..	..	2.6	2.9	1420	1280	...	...
G.G.	92	96	8.9	7.1	480	540	80	108
F.B.	84	90	4.4	4.6	545	520	96	80
D.B.	120	120	3.2	5.1	1284	794	172	106
T.A.	72	80	4.3	4.3	1160	950	81	65
J.M.	80	90	2.9	2.8	860	930	...	...
H.W.	110	115	2.5	2.0	1490	1690	167	159
P.R.	...	...	4.6	6.8	1066	541	219	38
W.P.	...	...	3.3	3.7	1280	1066	128	98
P.Z.	75	75	5.5	3.6	900	1000	73	80
W.M.	62	62	5.7	5.0	1360	1340	...	...
D.C.	...	...	3.0	3.5	1380	1200	...	...
A.L.	84	76	2.7	2.7	1520	1330	150	114
G.F.	104	108	5.5	7.0	560	430	56	38
F.S.	...	...	4.9	5.9	....	....	...	...
F.F.	90	95	3.3	2.9	1278	1225	148	168
N.M.	100	100	3.2	3.1	942	776	...	...
P.S.	66	78	3.2	6.8	1040	435	84	33
E.U.	...	...	3.1	4.0	1965	1025	109	82
H.A.	...	...	4.2	5.4	....	....	...	...
Mean	86	90.6	4.11	4.45	1124	944	125	92
Diff.	10.1		0.28		182		32.4	
t	5.29		1.04		2.77		8.67	
	P<0.001		0.400>P>0.200		0.025>P>0.010		P<0.001	

Although the parameters of systemic circulation which were measured did not show impressive changes, there was a trend toward a lower peripheral resistance after histamine. A lower resistance could lead to peripheral pooling of blood and a consequent drop in cardiac output. This was prevented by a rise in heart rate, thus homeostatic reflexes make it difficult to evaluate, quantitatively, changes in any one function.

3. *Pulmonary circulation*

To our knowledge, direct measurements of the effect of histamine on the pulmonary circulation in humans have not been reported. Different results have been observed in animals of different species, but it would be unwise to transfer such observations to humans. In rodents the predominant effect of histamine is bronchoconstriction; in cats, arterial vasoconstriction. In recent observations from this laboratory,[28] the intravenous injection of histamine in the anesthetized dog was found to induce an initial rise in pulmonary artery pressure, followed by a fall which was secondary to a drop in cardiac output. In the unanesthetized dog the increased pulmonary artery pressure has been interpreted as a passive result of an initial increase in venous return.[11, 26] In the isolated dog lung preparation, histamine also causes pulmonary hypertension; the increased resistance is apparently due to pulmonary vein constriction.[12] The effects of the drug on the airway volume and on the pulmonary blood volume are apparently independent of one another.[15] In rigidly controlled experimental conditions, however, with the lungs perfused artificially *in situ* through two separate cannulas, bronchoconstriction was associated with an increase in resistance to flow.[8]

Our findings in the pulmonary circulation were qualitatively similar to those in the systemic circulation. The wedge pressure showed no changes, suggesting that in our experiments pulmonary venous resistance did not increase. There were no significant changes in cardiac output, hence the hemodynamic effects of histamine on the pulmonary circulation are probably not passive results of its action on the systemic circulation. However, changes in distribution of blood may have occurred after the administration of histamine and between our consecutive measurements of cardiac output.

For the purpose of analysis of the circulatory effects of histamine, we have arbitrarily segregated those patients in whom the decrease in vital capacity was greater than 10 per cent. Although there are quantitative differences, the hemodynamic changes following administration of the drug in the subgroup of patients showing evidence of bronchoconstriction are essentially similar to those observed in the whole group. This suggests that, in our experiments, the bronchomotor effect of histamine has no measurable influence on the pulmonary arterial pressure.

The increased respiratory fluctuations in pulmonary arterial pressure have been interpreted as evidence of increased airway resistance.[2, 13, 14, 23] In order to analyze the mechanism of the respiratory swing, it is necessary to remove the influence of the intrathoracic pressure itself from the measurement of vascular pressure. To accomplish this the intrathoracic pressure must be subtracted algebraically from the observed gross vascular pressure, thus providing a "net" pulmonary artery pressure.[8] There was no difference

between the pulmonary artery pressure fluctuations of those patients who had evidence of bronchoconstriction and those who did not. and the pulmonary artery resistance decreased even in patients who showed bronchoconstriction; therefore, one must conclude that respiratory fluctuations do not reflect an effect of bronchoconstriction on pulmonary hemodynamics. Rather, it would appear, these fluctuations represent the algebraic sum of intrathoracic and intravascular pressure variations. This does not rule out the possibility that some types of bronchoconstriction could alter blood flow or resistance. The site of bronchial constriction or relaxation, whether involving primarily the large or small bronchi, must be determined if the relationship between bronchomotor tone and pulmonary hemodynamics is to be understood.[9] However, the bronchospastic effect of histamine has been shown to be similar to that of true asthma.[9] In view of this, the present studies cast doubt on the role of bronchospasm as a cause of increased pulmonary vascular resistance leading to pulmonary hypertension in patients with chronic asthma.

4. *Alveolar-arterial oxygen tension gradient*

A significant fall in arterial oxygen saturation was observed, but no change in arterial carbon dioxide tension. The alveolar-arterial oxygen tension gradient showed a rise. These changes in blood gas values have been reported by others,[10, 17, 20] who found a fall in arterial oxygen saturation after 1 to 1.5 mgm. of histamine in patients with heart and lung diseases. Tang[20] also observed a widening of the alveolar-arterial oxygen tension gradient following histamine. These workers were of the opinion that the observed changes in blood gas values were due to a thickening of the alveolar-capillary membrane.

The fall in arterial oxygen saturation seen in our patients was not produced by alveolar hypoventilation, as the arterial carbon dioxide tension was not elevated, nor was the alveolar ventilation changed after histamine. An increase in alveolar-arterial oxygen tension gradient might be due to a thickening of the alveolar-capillary membrane or an increase in venous admixture. Experiments have been carried out to study the possibility of venous admixture. After establishing the resting arterial oxygen saturation, patients were given 100 per cent oxygen to breathe following histamine administration. They all showed a rise in arterial oxygen saturation to 100 per cent during oxygen breathing. These experiments tend to exclude a venous admixture following histamine.[20] Animal experiments showing an increase in lung weight following histamine[12] suggest that the drug causes capillary dilatation, possibly also edema. This would increase the distance between the alveolar space and the hemoglobin and impair oxygen diffusion.

Transudation of plasma across the capillary wall and an increased concentration of hemoglobin have been noted by others, both in the systemic,[20, 22] and in the pulmonary circulation.[17] This effect was not noted in our patients, however, possibly because of the low dose of histamine used. The influence of histamine on arterial oxygen saturation and tension has already been applied in a test attempting to augment borderline central cyanosis in patients with various disorders.[5, 18, 27]

One probable explanation for the widening of the alveolar-arterial oxygen tension gradient observed in the present study is that a disturbance occurred in the ventilation-to-perfusion ratio. If perfusion increased greatly while ventilation did not, the alveolar-arterial oxygen tension gradient might be expected to increase. Hypoventilation alone does not seem a likely cause of the phenomenon, since the arterial carbon dioxide tension did not rise, but rather fell after histamine.

SUMMARY

Twenty-one patients with various chronic lung diseases have been studied. Ventilation and pulmonary hemodynamics have been observed following the subcutaneous administration of histamine phosphate. A pronounced decrease in maximal breathing capacity and vital capacity occurred in nine.

There was an increase in heart rate, a fall in systemic blood pressure and peripheral arterial resistance, but no change in cardiac output. A vasodilator effect of histamine was also demonstrated in the pulmonary circulation, with a fall in pulmonary artery mean pressure and pulmonary arterial resistance, but no change in pulmonary artery wedge pressure. The increase in bronchomotor tone produced by histamine in some patients did not measurably influence the pressures or resistance in the pulmonary circulation. The concept that pulmonary hypertension may be the direct effect of bronchoobstructive disease cannot be supported by these findings.

Arterial oxygen saturation fell, but little change occurred in arterial carbon dioxide tension. The alveolar-arterial oxygen tension gradient rose. The latter was probably the result of capillary dilatation and alteration of the ventilation: perfusion relationship produced by histamine.

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The Board of Editors

PETER ISACSON*

The Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia

CELLULAR TRANSFER OF ANTIBODY PRODUCTION FROM ADULT TO EMBRYO IN DOMESTIC FOWLS

INTRODUCTION

Simonsen[8] demonstrated that the intravenous inoculation of adult fowl spleen cells or peripheral white blood cells into chick embryos gave rise to splenic enlargement and a Coomb's positive hemolytic anemia in the recipient chick. He found that this effect was species specific, required viable cells from donors over 11 days of age for its initiation, and could be passaged from chick to chick at least nine times without apparent diminution of the phenomenon. He concluded that the reaction represented colonization of the recipient spleen by the implanted adult cells and that the adult cells produced antibodies against the antigens of the recipient chick, as manifested by the Coomb's positive chick red blood cells and hemolytic anemia. This thesis was further supported by the subsequent finding[4] that only slight splenic enlargement occurred when cells were transferred between antigenically similar inbred strains.

These findings are particularly relevant to the "clonal selection" theory of antibody formation of Burnet[3] in which it is postulated that an antigen serves to create a selective environment for functional replication of previously existing clones of specific antibody-producing cells. This theory would imply that cells capable of producing specific antibodies such as viral antihemagglutinating antibodies could be transferred from an immune adult donor to an embryonic recipient and then serially passaged from embryo to embryo under the influence of an appropriate antigenic environment.

The work to be presented was prompted by a desire to test this possibility using influenza virus as an antigen and the method described by Simonsen as the test system.

MATERIALS AND METHODS

Fowl lines. The lines principally used in these experiments have been White Leghorns and Australorps obtained from a commercial hatchery. Eggs were placed in a 35° C. incubator until 24 hours after hatching and then transferred to an electric brooder. The

* At present Instructor in Section of Preventive Medicine, Yale University School of Medicine.

inbred lines were obtained through the courtesy of the Animal Health Division of the Commonwealth Scientific and Industrial Research Organization. Each line has been propagated by successive matings of full and half sibs and has an inbreeding coefficient of approximately 80 per cent. Details of the method have been presented by Skaller.[9]

Antigen. The antigen used was Melbourne (MEL), an A influenza strain first isolated in Melbourne in 1935. The virus was grown in the allantoic cavity of chick embryos and freshly harvested suspensions were placed in a 56° C. water bath for one hour to destroy infectivity. Infectivity titres prior to heating ranged between $10^{8.8}$ and $10^{7.8}$ EID_{50} per ml. in the allantoic cavity of the chick embryo.

Preparation of cell inocula. Whole blood was obtained by cardiac puncture through a heparinized syringe. The cells were washed in saline and the buffy coat removed. Leukocyte counts were performed in a haemocytometer chamber and the cells diluted in normal saline to the desired concentration. Spleens from adult fowls or chicks were removed aseptically under chloroform anesthesia. The capsule was stripped off and cells teased apart with fine needles into ice cold saline. The suspension was then filtered through a loose wire mesh under light pressure, washed three times in normal saline, and resuspended to the desired cell concentration in normal saline after counting in the haemocytometer chamber. Penicillin and streptomycin were added to make a final concentration of 500 units of penicillin and 500 micrograms of streptomycin per ml. All cell suspensions were kept at 4° C. and inoculated within one hour of preparation. When mixtures of cell suspensions from different donors were inoculated, the suspensions were prepared separately and mixed together in equal volumes immediately prior to inoculation.

Inoculation of eggs. According to the method of Beveridge and Burnet.[2] The volume of the inoculum in all instances was 0.05 ml.

Antibody titrations. Embryos were bled by removing an area of the shell, clearing the membrane with sterile glycerine, and withdrawing blood by puncture from a chorio-allantoic artery. Hatched chickens were bled by cardiac puncture. The sera were separated and heated at 56° C. for 30 minutes. Although MEL virus is relatively insensitive to mucoid inhibitors, most adult fowl sera and occasional chick sera inhibit MEL in low dilutions in an antihemagglutinin (AHA) titration. To remove this non-specific inhibition, two volumes of M/100 potassium periodate were added to the sera, the mixture was allowed to stand for two hours at room temperature, and two volumes of 50 per cent glycerol were added to make a final serum dilution of 1:5. The AHA titrations were performed in the standard fashion with the exceptions that 2 to 2.5 agglutinating doses of virus and 0.5 per cent adult fowl red blood cells were used. A hyperimmune fowl serum of known potency was included in each test. All results presented in the same table or figure were performed on the same day.

Spleen weights. Spleens from embryos and young chicks were removed after exsanguination. They were dissected cleanly from adherent tissue, allowed to stand for 30 minutes on filter paper, and weighed to the nearest milligram.

RESULTS

COMPOSITION OF CELL INOCULA

The cell concentrations referred to in this article include all cell types excluding mature red blood cells found in the teased spleen cell suspensions

and all forms of leukocytes found in the peripheral blood. Since a vast body of evidence has incriminated cells of the lymphocyte and plasma cell series as antibody producers, it is of interest to know the relative proportion of these cell types in the inocula. Smears of spleen cell suspensions and peripheral blood were prepared, stained with Leishman's stain, and cell ratios determined after counting 2,000 to 5,000 cells. The morphologic criteria used for the identification of immature forms correspond to those of Makinodan, Ruth, and Wolfe.[8] Table 1 lists the percentage of these cells found in inocula

TABLE 1. CELL TYPES IN INOCULATING SUSPENSION

		Per cent cell type				
		Blast cell	*Prolympho-cyte*	*Lympho-cyte*	*Proplasma-cyte*	*Plasmacyte*
		Spleen cell suspension				
Normal	1	0.1	12.28	28.0	1.69	1.74
	2	0.8	20.1	29.0	0.9	1.2
	3	1.1	9.9	32.0	1.9	1.7
Immune	1	2.4	14.4	24.4	3.1	4.1
	2	1.9	11.5	20.0	1.5	2.5
		Peripheral leukocyte suspension				
Normal	1	0.0	10.0	43.5	0.0	0.5
	2	0.0	4.2	38.6	0.0	0.0
	3	0.0	6.8	60.6	0.08	0.8
Immune	1	0.0	4.0	52.4	0.0	0.0

prepared from normal adult nonimmunized fowls and also from adult fowls which had received two intravenous inoculations of heat-killed MEL virus at an interval of one month and were sacrificed 24 hours after the second inoculation. For the spleen cell suspensions, the figures represent per cents of all cell types found excluding mature red blood cells. For peripheral blood, the figures represent per cents of all leukocytes.

As would be expected, the results indicate that the spleen cell suspensions contained a variety of developmental stages in the lymphocyte and plasma cell series. Inoculation of 10^4 or more cells would contain a plentiful and representative supply of developing stages of these cells. No cells of an earlier stage than large lymphocytes were identified on a survey of 5,000 leukocytes of the peripheral blood. While this does not exclude the possibility that inocula of 10^4 cells may contain less mature forms, it makes the uniform appearance of immature forms in a series of inocula of this concentration unlikely.

GROSS AND MICROSCOPIC FINDINGS AFTER CELL TRANSFER

Spleen weights after inoculation. Inoculation of adult fowl spleen cells or peripheral leukocytes intravenously into chick embryos may give rise to massive enlargement of the recipient spleen. Figure 1 illustrates the magnitude of the difference obtained when 10^7 spleen cells from a normal adult fowl were inoculated into a 14-day-old embryo. The experimental spleen was removed five days after inoculation and is shown together with a spleen from a normal embryo of the same age.

The time course of enlargement after inoculation is shown in Figure 2. Embryos of 14 days of incubation were given 2 x 10^7 spleen cells intravenously, and controls of the same age were given equal volumes of normal saline. Each point on the graph represents an average of at least six spleen weights in milligrams. At one day after inoculation there was no apparent difference between the average spleen weights of the two groups. On the second post-inoculation day the experimental spleens were slightly heavier, but the numbers involved were too small to permit a valid comparison. By the third day the spleens of the experimental group were enlarged two times those of the control group. Progressive enlargement continued, reaching a maximum around the sixth day and thereafter declined. By the 16th day after inoculation the spleens of the two groups were comparable in size. It should be noted, however, that after the first week a high mortality, presumably from hemolytic anemia, was present in the inoculated group. Hemolytic anemia and spleen weights show a crude parallel, therefore a bias towards smaller spleens may have been present in the survivors after one week.

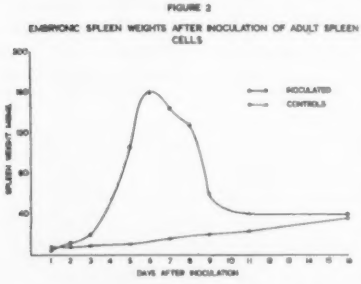

FIG. 2. Spleen weights from embryos inoculated with 2 x 10^7 adult fowl cells at 14 days of incubation. Controls represent spleen weight from embryos of the same age group given normal saline intravenously.

Factors influencing splenic enlargement. The species specificity of this phenomenon was tested by the inoculation of rabbit and mouse spleen cells, human peripheral blood and also by Hela cells of a strain being routinely used in this laboratory for adenovirus studies. The age specificity of the donor was also determined by the inoculation of spleen cell suspensions from fowl donors of varying ages. An indication of the viability requirements of the inoculated cells was obtained by subjecting spleen cells from an adult

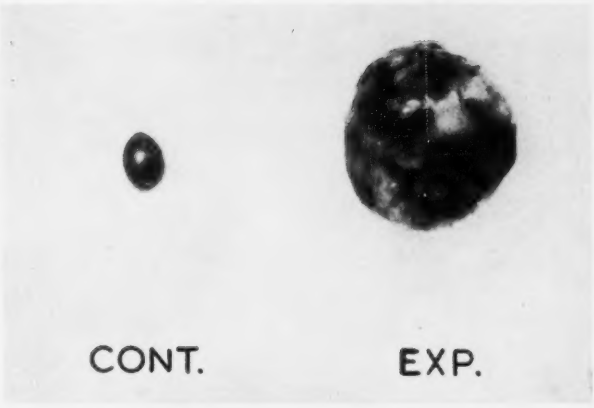

FIG. 1. Enlarged spleen from a 19-day-old chick embryo inoculated with 10^7 spleen cells five days previously. Shown together with a spleen from a normal 19-day-old embryo.

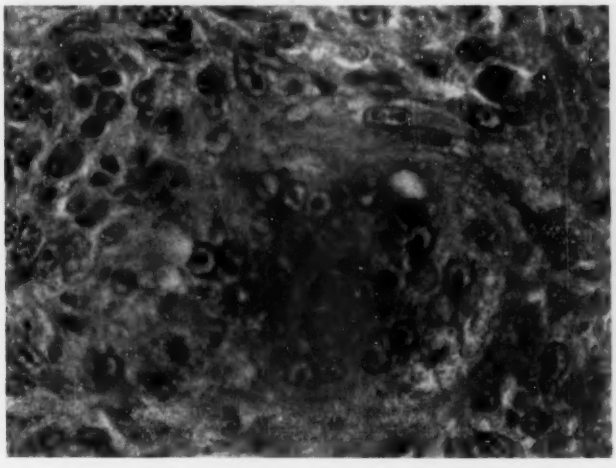

FIG. 3. Spleen from a 14-day-old embryo inoculated with 3×10^6 adult spleen cells two days previously. Hemotoxylin and eosin (x1,100).

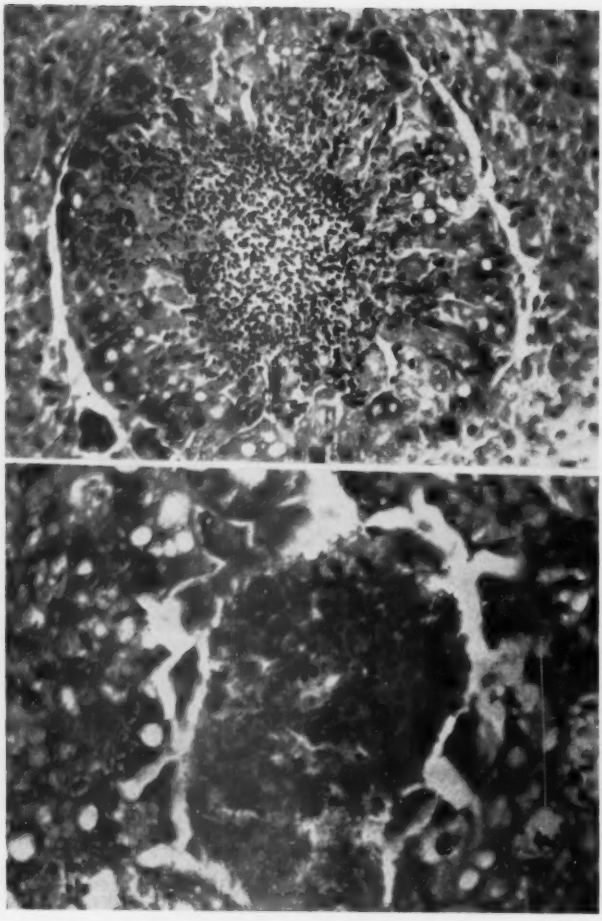

FIG. 4. Spleen from a 15-day-old embryo inoculated with 3×10^6 adult spleen cells three days previously. Unna Pappenheim (x500).

FIG. 5. Same spleen as Fig. 4. Hematoxylin and eosin (x600).

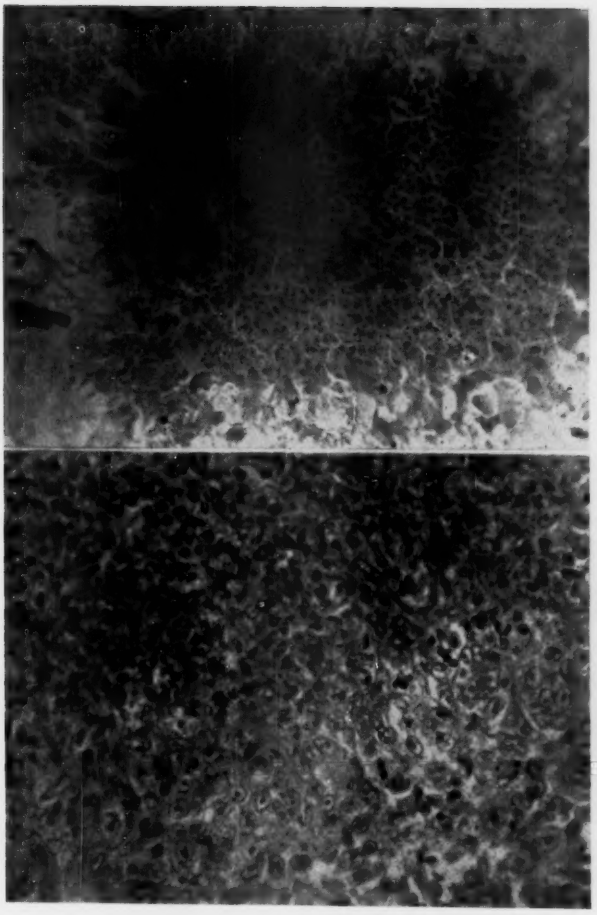

FIG. 6. Spleen from 17-day-old embryo inoculated with 4 x 10^6 adult spleen cells five days previously. Hematoxylin and eosin (x300).

FIG. 7. Spleen from a 19-day-old embryo inoculated with 4 x 10^6 adult spleen cells seven days previously. Hematoxylin and eosin (x525).

donor to freezing and thawing three times and also to heating at 56° C. for 20 minutes before inoculation. The results are summarized in Table 2. Of the inocula tested, only untreated cells from fowls 10 days of age or older were capable of initiating significant splenic enlargement. Cells from the 10-day-old donors gave rise to a lesser degree of splenic enlargement than

TABLE 2. FACTORS INFLUENCING SPLENIC ENLARGEMENT

Cell inoculum	*Donor*	*No. cells inoculated*	*Spleen weights in mgms.*		
			No. tested	*Range*	*Average*
None	—	—	50	5-15	8.0
Spleen	Adult rabbit	10^6	10	5-16	8.8
Spleen	Adult mouse	10^6	15	6-12	9.4
Peripheral leukocytes	Adult human	2×10^5	25	6-12	8.5
Hela cells	Human	3×10^5	4	10-14	11.0
Spleen frozen and thawed	10-wk. adult fowl	*10^6	20	6-15	9.8
Spleen heated 56° C.	10-wk. adult fowl	*10^6	20	7-15	10.0
Spleen	10-wk. adult fowl	10^6	30	45-320	182.0
Spleen	10-day chick	5×10^5	25	7-64	32.4
Spleen	5-day chick	10^6	15	4-14	8.5
Spleen	1-day chick	4×10^5	10	6-12	7.0
Spleen	19-day embryo chick	2×10^6	10	5-12	8.6

* Cell count prior to treatment.

a comparable cell concentration from more mature donors, indicating that there may be a gradual increase with age in the ability of the donor cells to initiate this phenomenon. These findings of species and age specificity and the necessity for viable cells are completely in accord with the data of Simonsen.[8]

The number of cells required to induce splenic enlargement is of interest, and attempts to determine this number were made by preparing serial dilutions of spleen and peripheral leukocyte suspensions from the same fowl and

inoculating these into 13-day-old embryos. Results are shown in Table 3. Totals of 3.75×10^4 peripheral leukocytes per inoculum were required to produce significant enlargement of the spleen in a majority of the recipients. Beyond this point, higher concentrations of cells tended to produce more rapid splenic enlargement and somewhat heavier spleens, but this relationship is not clear cut. In one instance an enlarged, nodular spleen was found in a recipient of only 4.7×10^3 spleen cells. Thus the enlargement of the

TABLE 3. NUMBER OF CELLS REQUIRED TO INDUCE SPLENIC ENLARGEMENT

Source	*No. cells inoculated*	*Spleen weights in mgms. 6 days after inoculation*
Spleen	3.0×10^5	200, 101, 74, 69
	7.5×10^4	120, 70, 61, 49
	3.75×10^4	106, 76, 64, 48, 17
	1.87×10^4	20, 16, 15, 14, 9
	9.3×10^3	14, 12, 12, 8
	4.7×10^3	38, 11, 11, 10, 9
Peripheral leukocytes	3.12×10^5	312, 171, 76, 49
	7.8×10^4	207, 193, 71, 68
	3.9×10^4	78, 58, 49
	1.95×10^4	49, 38, 34 11, 8
	9.7×10^3	16, 13, 12, 10, 9, 8
Normals	—	12, 11, 11, 10, 7, 5

recipient spleen gives only a crude indication of the number of cells inoculated. The data suggest that peripheral leukocytes may be slightly more effective than spleen cell suspensions. If Table 1 is taken into consideration, however, and attention focused only upon cells of the lymphocyte and plasma cell series, no significant difference between the two types of suspensions can be found. The observation that splenic enlargement can be initiated by 1.95×10^4 peripheral blood leukocytes leads to the impression that mature cells can initiate the process, and this is strengthened by the finding that spleen cell suspensions, containing many forms of developing cells, are no more effective in causing splenic enlargement.

The age of the recipient embryo at the time of inoculation exerted a marked influence upon the type and degree of splenic enlargement obtained. Table 4 shows the resultant spleen weights when 5×10^6 from the same adult donor fowl were inoculated into embryos from 11 to 20 days of incubation. Splenic enlargement occurred in the recipients of all age groups tested but embryos from 11-15 days at the time of inoculation showed spleen

weights from two to three times greater than those of the older embryos. Aside from the greater weight in the younger group, their spleens also showed gross irregularity of the surface. When embryos in this group were sacrificed 3-4 days after inoculation, raised areas approximately 1 mm. in diameter were found scattered over the surface of the spleen. By the 5th to 6th day these areas appeared as yellowish white, glistening, well-circumscribed nodules quite distinct from the surrounding splenic tissue. On teasing the spleen with fine needles these nodules separated readily, and on further dissection of the nodules themselves a hard, white, central core could be shelled out.

TABLE 4. INFLUENCE OF RECIPIENT AGE ON SPLENIC ENLARGEMENT

Age of embryo at inoculation	*Spleen weights in mgms. 6 days after inoculation*		
Days of incubation	*No. tested*	*Range*	*Average*
11	21	36-195	92
13	19	54-312	178
15	16	46-270	162
17	25	31-84	67
20	18	49-91	74

The spleens of the older (17-20 days) recipients showed smooth surfaces and symmetrical enlargement throughout, with none of the gross features as described above for the younger embryos. The differences in total weight and morphological appearance between the younger and older age groups cannot be ascribed merely to dilution of the inoculated cells in the larger blood volume of the older recipients. Although there is a four-fold increase in whole embryonic weight between the 12th and 18th days, ten-fold differences in cell concentration between the inocula given to younger and older embryos gave rise to results identical to those just described.

Histological findings. For detailed description of the embryology of the normal chicken spleen with particular reference to the hematopoietic cells the reader is referred to Sandreuter.[7] In brief, granulopoiesis is present in the spleen by the 10th embryonic day, reaching a peak of activity at 14-18 days and thereafter gradually declining. Lymphocytic activity can be noted in 12-day-old spleens but does not become pronounced until 16-18 days of embryonic life and increases after hatching. Erythropoiesis is seen in the embryonic spleen but after hatching this function is taken over entirely by the bone marrow. These various hematopoietic elements are present diffusely

within the spleen, and well-circumscribed, focal or nodular collections of large numbers of hematopoietic cells are not present during embryonic life. It is noteworthy that plasma cells are found neither in liver, spleen, bone marrow, nor peripheral blood during embryonic life and do not make their appearance in any of these sites until 20 days after hatching.

The histological appearance of the spleens from embryos inoculated with adult cells was again dependent on the age of the recipient at inoculation with marked differences being observed between embryos inoculated at 11-15 and 17-20 days of incubation. When 12-day embryos were used as recipients, the following sequence of events was seen: one day after inoculation the normal architecture of the spleen was not disturbed but large, actively mitotic cells with pyrinophilic cytoplasm were found scattered throughout the sinusoids. Differentiation between this picture and that of a normal spleen of the same age was not easily provided, however. Two days after inoculation occasional small focal collections of these cells could be seen. Figure 3 is a microphotograph of such a focal collection. Mitotic figures are present and the cells are surrounded by an eosinophilic collar. The genesis of the surrounding material cannot be stated with certainty but the picture could be consistent with early proliferation of an embolic focus within a degenerating arteriole. By the third post-inoculation day extensive replication occurred and large focal collections of basophilic cells were present, often large enough to be discerned grossly when near the surface of the spleen. An Unna-Pappenheim stain of this stage is shown in Figure 4, illustrating the marked difference in the staining characteristics as compared to the surrounding cells. A higher magnification of the edge of the same cell focus is shown in Figure 5. At this point the cells show no mitoses and the nuclei are undergoing pyknosis. The lack of significant reaction in the surrounding tissue is also apparent. Figure 6 is illustrative of the situation at five days after inoculation. By this point frank necrosis of the cell mass has begun. The necrosis proceeds from the periphery inwards, leaving structurally intact cells only in the centre. Around the periphery are radially arranged, vacuolated epithelioid cells. The origin of the cells is obscure, but in structure and staining characteristics they resemble far more closely the surrounding embryonic spleen cells rather than the cells in the centre of the mass. By seven days necrosis is almost complete, leaving a cavity filled with eosinophilic debris and only a few structurally intact cells. This stage is shown in Figure 7. It represents the point at which spleen size no longer increased.

Thus the sequence of events was initially active proliferation from a small focus of cells leading to large nodular collections and later peripheral reaction and necrosis with final complete cell destruction. The histological

features of the later stages are entirely what would be expected if the embryonic spleen were considered to be confining, localizing, and finally rejecting an implant of foreign tissue.

The histology of spleen from older recipients was similar to that described by Simonsen[8] and consisted primarily in the appearance of numerous actively mitotic basophilic reticuloendothelial cells. Disintegrating polymorphonuclear leukocytes were also found as were occasionally syncytial giant cell formations. The large foci of mononuclear cells with subsequent necrosis as described in the younger embryos were not found in spleens from recipients 17-20 days old at the time of inoculation.

TABLE 5. INFLUENCE OF INBREEDING ON SPLENIC ENLARGEMENT

Donor adult	*Recipient embryo*	*Spleen weights in mgms. 5 days after inoculation*
Inbred	Inbred	24, 12, 13, 20, 18, 24, 34, 24
	Noninbred	278, 166, 360, 250, 144, 190, 205
Noninbred	Inbred	148, 76, 90, 89
	Noninbred	209, 49, 78, 29, 178, 91

Influence of genetic disparity. Cock and Simonsen[4] were able to demonstrate that when cell transfer was performed between donor and recipient of highly inbred fowl lines, splenic enlargement was significantly less than when the same cells were inoculated into embryos of crossed lines. These workers used newly hatched chicks as recipients, however, at which age the type and degree of splenic enlargement is less pronounced.

In order to determine whether the findings in younger embryos are also influenced by genetic similarity, 10^7 spleen cells from an adult female inbred donor were inoculated intravenously into her own eggs, eggs from full sisters inseminated by the same cockerel, and also into nonrelated eggs of the same age. Eggs of the inbred strain were also inoculated with spleen cells from an unrelated donor. Results are given in Table 5. Inbred embryos receiving cells from a donor of the same strain showed very little splenic enlargement as compared to uninoculated eggs, while the same cell concentration from the same donor caused massive splenic enlargement in the non-

inbred recipients. That the inbred embryos could respond is shown by the spleen weights of inbred recipients given spleen cells from an unrelated donor. The spleens became enlarged to the same degree as those of noninbred embryos receiving the same cell inoculum. These results therefore confirm the finding of Cock and Simonsen and also extend them to include the type of splenic enlargement found in young embryonic recipients.

Possibilities of infection. The gross appearance of the spleen resembled the findings in certain instances of infection of the embryo with microorganisms. Intensive search by histological and cultural methods failed to reveal any bacterial, fungal, or parasitic contaminant either in the inocula or the recipient spleens. Viral diseases are more difficult to rule out. Forms of avian lymphomatosis are prevalent in many fowl flocks and may resemble many of the features described after cell transfer. The accumulated evidences of age specificity of both donor and recipient, requirement for viable cells, effect of inbreeding, absence of demonstrable lesions in the donors, and the correlation with antibody production to be presented in the following section all serve to make the possibility of transmission of virual leukosis unlikely.

ANTIBODY FORMATION AFTER CELL TRANSFER

Transfer of spleen cells from immunized donors

Time course of antibody production. When the donor adult fowls were previously stimulated with heat-killed MEL virus, transfer of spleen cells to embryos resulted in the appearance of MEL antihemagglutinin (AHA) antibodies in the sera of the recipients. The time interval required for the appearance of these antibodies is shown in Figure 8. In this experiment a 10-week-old female donor was given two intravenous inoculations of 1.0 ml. of undiluted heated MEL virus with an interval of one month between inoculations. The fowl was sacrificed 24 hours after the second antigenic stimulus and inocula of 10^7 cells were transferred intravenously into 13-day-old embryos. Embryos and newly hatched chicks were sacrificed at the intervals shown and AHA titrations performed on the individual sera. As shown in the figure, no antibodies could be detected in the sera of recipients sacrificed on the first two days after inoculation. This complete absence of detectable antibodies for a 2-day period served effectively to rule out the possibility that any subsequent antibody was derived from passive transfer. Antibodies began to appear on the third day in low titres, reached the highest levels on the 6th day and thereafter showed a gradual decline, although levels could be detected as long as two weeks after inoculation. The curve

shows a general resemblance to the curve of spleen weights shown in Figure 2, but the antibody titres did not drop with the rapidity exhibited by the spleen weights.

Factors influencing antibody production after transfer. A procedure consisting of immunization of a donor, removal of spleen cells, and transfer to embryonic recipients obviously involves a number of complex steps, and the amount of antibody eventually found in the sera of the recipients is influenced by a wide variety of factors. The requirements of age and species

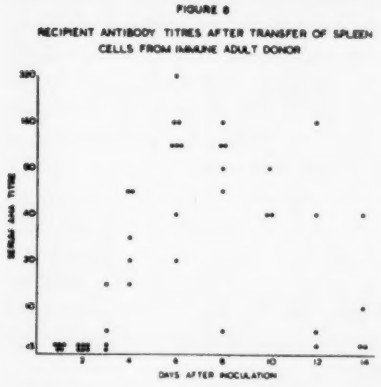
FIGURE 8
RECIPIENT ANTIBODY TITRES AFTER TRANSFER OF SPLEEN CELLS FROM IMMUNE ADULT DONOR
SERUM AHA TITRE
DAYS AFTER INOCULATION

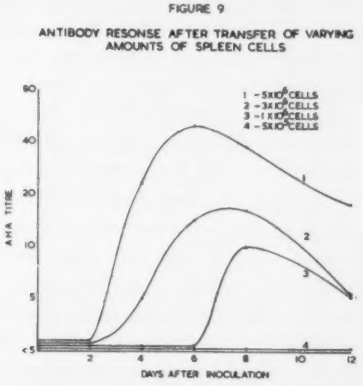

FIG. 8. Recipient MEL AHA titres after transfer of 10^7 spleen cells from an adult fowl immunized with heat killed MEL virus. Each dot represents a separate recipient.
FIG. 9. Recipient MEL AHA titres after transfer of varying amounts of spleen cells from an adult fowl immunized with heat killed MEL virus. Each dot represents an average of 5-8 determinations.

specificity and cell viability as shown in Table 2 for splenic enlargement also applied to the production of MEL AHA antibodies. Transfer of antibody production could not be obtained with heated or frozen and thawed cells, cells of different species, or cells from embryonic or neonatal donors.

The nature of the immunization of the donor, the presence or absence of antigen added to the spleen cells *in vitro* prior to transfer, and the age of the recipient embryo might also be expected to influence the degree of antibody response obtained. Table 6 summarizes the results from a series of transfer experiments designed to test these factors. The donor fowls were all females from 10 to 15 weeks old at the time of sacrifice. The concentrations of spleen cells were 5 to 6 x 10^6 per inoculum in all instances. In some cases heated MEL virus was added to the inocula to make a final concentration of 1:50.

When the donor fowl was given a primary intravenous or intraperitoneal stimulus and an intravenous booster after an interval of one month, transfer of spleen cells 24 hours after the second stimulus resulted in antibody formation in all recipients regardless of age or the presence or absence of antigen added *in vitro*. That the route of immunization was important was shown by the failure to transfer antibody formation when the second stimulus was given intraperitoneally. When the interval between stimuli of the donor was shortened to one week, the age of the recipient embryo assumed importance. Antibodies were found consistently and in a higher titre in embryos from 11-15 days at the time of inoculation as compared to recipients from 17-20 days of age. If no secondary stimulus was given *in vivo*, the addition of antigen *in vitro* was necessary and the influence of the age of the recipient became more important. In this instance only the younger recipients who had received cells plus antigen showed antibodies in their sera. When the donor fowl was sacrificed 12 hours after the primary stimulus, no antibodies could be detected in the sera of any recipients.

The results clearly indicate that younger embryos (11-15) served as more effective recipients for cellular transfer of antibody formation than did older (17-20 days) embryos. This division by age group follows closely the pattern of splenic enlargement by age group presented in the previous section. The data also show that antigen (MEL) could exert a marked stimulatory effect when added *in vitro* to previously stimulated cells although *in vivo* second stimuli were more effective.

The number of cells necessary to induce AHA antibody formation in recipients was determined by the inoculation of serial dilutions of spleen cells. The adult donor was given two intravenous stimuli of heat-killed MEL at a one-month interval, sacrificed 24 hours after the last stimulus, and spleen cells transferred to 13-day-old embryos. The results are shown in graphic form in Figure 9. Detectable antibodies were found in recipients receiving 10^6 or more spleen cells. The time of appearance of antibodies also showed a direct relationship to cell concentration. Antibodies appeared earlier and reached a more rapid peak in the recipients of the more concentrated cell suspensions.

A comparison of the relative effectiveness of spleen and peripheral leukocyte suspensions was also attempted by inoculating serial dilutions of these suspensions into 13-day embryos. While 10^6 spleen cells resulted in detectable antibody formation in the recipients, concentrations of 10^8 peripheral leukocytes per inoculum gave rise only to sporadic and low titred antibody levels in the recipients. This is in contrast to the results shown in Table 3 in which spleen and peripheral leukocyte suspensions appeared equally effective in initiating the phenomenon of splenic enlargement.

TABLE 6. FACTORS INFLUENCING ANTIBODY PRODUCTION IN RECIPIENTS AFTER CELL TRANSFER

Route of primary stimulus	*Interval between primary and secondary stimuli*	*Route of secondary stimulus*	*Interval between last stimulus and sacrifice*	*MEL* in vitro	*Number of recipients*	*Age of recipient embryo—days of incubation*	*Antibodies in recipients*
Intravenous or intraperitoneal	one month	intravenous	24 hours	present or absent	36	11-15	++
					49	17-20	++
Intravenous	one month	intraperitoneal	2-4 days	present or absent	14	17-20	0
Intravenous	one week	intravenous	24 hours	present	28	11-15	++
				or absent	18	17-20	±
Intravenous	—	—	one month	present	27	11-15	++
					19	17-20	0
				absent	14	11-15	0
					12	17-20	0
Intravenous	—	—	12 hours	present or absent	16	11-15	0
					10	17-20	0

++ Antibodies detectable in all recipients. ± Antibodies detectable in less than half of recipients.
0 Antibodies not detectable in any recipients.

Transfer of cells from nonimmunized donors

Attempts at initiation of antibody formation were made by transfer of spleen cells from normal, nonimmunized adult donors with antigen added to the cell suspension *in vitro* immediately prior to inoculation. Cell concentrations were varied between 1 x 10^5 and 2 x 10^7 cells per inoculum. The concentration of antigen was varied between 10^{-1} and 10^{-5}, the dilutions representing heated allantoic fluid virus per unit of inoculating suspension. Dilution of the cell suspension in autologous and homologous sera and

TABLE 7. ATTEMPTED PASSAGE OF ANTIBODY-PRODUCING CAPACITY

Passage level	*Donor*	*Recipients*	*No. cells inoculated*	*AHA titres recipients at 5 days*	*Spleen weights recipients at 5 days*
1	immune adult fowl	13 d embryos	2 x 10^6	40, 120, 60 90, 20	148, 76, 52, 48, 60
2	1st passage recipients	13 d embryos	4 x 10^6	all less than 5	166, 22, 184, 46, 94, 36
3	2nd passage recipients	13 d embryos	4 x 10^6	all less than 5	101, 30, 89, 75, 59

concurrent administration of adult liver cells was also attempted. Both young and old age groups of embryos were used as recipients but the majority were in the 11-13-day age group since the previous data had indicated that this was the most sensitive age.

Of 328 recipient sera examined from experiments of this nature, only five showed detectable levels of MEL AHA antibody. The attempts were thus considered to be negative.

Attempts at serial passage of antibody formation

If functional replication of adult antibody-producing cells can occur within the spleen of a chick embryo, it would be reasonable to expect that these cells might then be serially passaged from embryo to embryo with demonstrable antibodies at each passage level. This possibility was tested by inoculating embryos with spleen cells from an immune donor, removing the recipient spleens after varying time periods, and inoculating those cells into further groups of embryos.

A representative example of these attempts is given in Table 7. Embryos of 13 days of incubation were inoculated with 4 x 10^6 spleen cells from an immune adult donor. After 4 days, serum AHA titres of the recipients

ranged from 30 to 240. At this point the recipient spleens were removed, a cell suspension containing 6 x 10^6 cells per 0.05 ml. prepared and inoculated into a further group of 13-day embryos. The spleens of this group of recipients showed comparable splenic enlargement, but no antibodies to MEL could be detected in their sera. One further passage again resulted in splenic enlargement of the same magnitude as the initial passage but antibodies remained undetectable.

A number of comparatively simple technical reasons could explain this failure to transfer antibody formation from embryo to embryo. The per cent of viable donor spleen cells which actually reach the recipient spleen after intravenous inoculation on first passage cannot be estimated with accuracy, but may be quite small. Thus an overwhelming dilution factor on first passage could be responsible for the failure of subsequent transfer. In an attempt to overcome this possible drawback, spleens were pooled from large numbers of first passage embryonic recipients and cell concentrations of up to 10^8 were inoculated into further embryonic recipients. Cell suspensions of this concentration are highly lethal to embryos, but of those surviving, none showed detectable levels of antibody.

Histological studies as shown in the previous section had indicated that some degree of cellular degeneration was apparent in recipient spleens as early as 3-4 days after inoculation of adult cells. Passage after too long an interval might therefore fail because of loss of cellular viability. For this reason second passage was attempted during 1-, 2-, and 3-day intervals after the initial cell transfer, again with negative results.

Results were also negative when passage was attempted in the presence of varying amounts of antigen and when normal adult fowl serum was added to the inoculum.

DISCUSSION

The postulated ability of adult reticulo-endothelial cells to colonize recipient and produce injurious antibodies against the antigens of the recipient has been termed the "donor vs. host" reaction. Phenomena of this general nature have been reported in various animal species using both embryos and irradiated adults as recipients of the implanted adult cells. Although the present study was not primarily designed to investigate this aspect, many of the findings confirm those of Simonsen[8] and lend further support to the thesis of immune response of donor to recipient. Firstly, enlargement of the recipient chick embryo spleen occurred only when cells potentially capable of producing antibodies were inoculated and it occurred only when cells were taken from a donor old enough to respond to antigenic

stimulation itself. Procedures which destroyed cells such as heating or freezing and thawing abolished the effect. When antigenic differences between donor and recipient were minimized by the use of inbred strains of chickens, transfer of spleen cells caused very little splenic enlargement in the recipient. Finally, this effect could be passaged from chick embryo to chick embryo indicating that the factor responsible for enlargement could undergo functional replication. These findings, together with Simonsen's demonstration that an antibody capable of coating the recipient red blood cells was found in the recipient, all suggest that the adult cells implanted in the recipient spleen were stimulated to reproduction and antibody formation by the antigenic differences of the recipient.

This cannot be considered a proven fact, however, for the crucial test of marking or tagging the implanted cells and subsequently identifying them as such in the recipient spleen has not yet been performed in this system. Thus the possibility remains open that the whole phenomenon represents inductive changes in the recipient spleen rather than multiplication of implanted adult cells. Such a mechanism has been postulated by Ebert,[6] and Andres[1] has presented more direct evidence of subcellular growth stimulating factors in the chick embryo. The histological features found in the present work after inoculation of younger age embryos speak against induction, however. At five days after inoculation the embryonic spleen gave the appearance of actively rejecting the cell focus. A reaction as marked and prompt as this would be difficult to imagine if the cell foci were considered to be originating as inductive response of the embryo's own spleen. Perhaps the simplest and most tenable way to avoid this apparent controversy between "induction" and "foreign cell proliferation" is to suggest that both mechanisms occur. Subcellular organ specific growth stimulating factors may be quite important in ontogeny, but may be relatively independent of the phenomena observed after intravenous inoculation of viable adult reticulo-endothelial cells.

Of particular interest in the present study is the marked influence of the age of the recipient embryo upon both splenic enlargement and cellular transfer of antibody production. Embryos of the younger age group (11-15 days) showed not only larger spleens after inoculation with adult spleen cells as compared to the older age group (17-20 days), but also showed the formation of foci of rapidly proliferating mononuclear cells large enough to cause gross nodularity of the spleen. There is nothing in the data to give conclusive reasons for this age difference, but the histological features found 5-7 days after transfer of adult cells to the younger embryos offer strong hints. As mentioned previously, at this point the histological picture is one of active rejection of the cell foci by the recipient spleen. This indicates that embryos as young as 16 days of incubation may possess at least one form of

protective response. It is not unreasonable to expect that this ability to reject foreign implants would show an increase in parallel with the age of the embryo. The reason for the differences in response according to age at inoculation could then be more readily explained. When embryos of the younger age group were inoculated with adult cells, the implanted cells were allowed to undergo almost unrestricted multiplication since the embryo at this age had very little ability to reject the cells. As the embryo aged, and the antigenic mass of the cell foci became large enough, a reaction occurred on the part of the host to the cell mass, and active destruction of the cell foci occurred. When embryos of an older age group were inoculated, multiplication of the implanted cells was more restricted because of the embryo's increasing ability to reject foreign cells and the large nodular foci of cells simply had no chance to form. Thus both the total weight and histological picture were different in recipients of the younger and older age groups.

The finding that MEL AHA antibodies could be transferred with greater ease to younger recipients is entirely consistent with this approach. When the donor fowl was sub-optimally stimulated (i.e. only one *in vivo* antigenic stimulus) and spleen cells plus MEL transferred to recipients of varying ages, antibodies appeared in only the younger age group recipients. It is very tempting to explain this on the same basis as given for the gross and histological differences by age group. It could be assumed that MEL AHA antibody-producing cells underwent functional replication in younger embryos, thereby producing enough antibody to be detectable in the sera. In the older embryos, antibodies did not appear because of the limited or absent functional replication of cells. While this explanation is consistent with the observed facts, it is also entirely possible that the observed differences in antibody production according to age are due to a longer life span of individual cells in the younger embryos rather than actual functional replication of the cells.

The number of cells required to induce splenic enlargement is of interest in view of Burnet's "clonal selection" hypothesis (1957). An essential feature of this theoretical approach is the requirement of clones of cells which are preadapted to produce only one specific antibody type. The presence of the corresponding antigen then allows for selective replication of these pre-existent antibody-producing cells in a clonal fashion. Since an adult fowl may respond to a wide variety of antigens, it would be necessary on the basis of this theory that a correspondingly wide variety of pre-adapted clones be represented in the fowl reticulo-endothelial system. Any single clone or cellular representative would then be present in very small proportion, and in order to insure the presence of any given cell type in an inoculum a large number of cells would have to be included.

In the present study, it was found that as few as 15,000 peripheral leucocytes could initiate this phenomenon. Of these 15,000, many are of a cell type (polymorphonuclear) not usually considered to be involved in antibody production. A certain proportion may have lost viability during manipulation and of the viable cells the number which actually reach the recipient spleen is undoubtedly further reduced because of filtration in lungs, bone marrow, and other chick organs. Therefore the number of cells required to initiate splenic enlargement is too small to be entirely consistent with all aspects of the clonal selection hypothesis.

When normal, nonimmunized adult fowl spleen cells were mixed with MEL *in vitro* and inoculated into young embryos, detectable levels of MEL AHA antibodies could not be consistently found in the sera of the recipients. A number of possible explanations could be advanced to account for this failure. It should be noted, however, that Trnka[10] has succeeded in initiating antibody production in newly hatched chicks after inoculation of adult fowl spleen cells exposed *in vitro* to bacterial antigens. The failure to initiate MEL antibody production *in vitro* in the present work may therefore be related to the type of antigen used and/or a lack of sensitivity of the test system, and a more elaborate explanation need not necessarily be invoked.

The failure to transmit MEL AHA antibody formation for more than one passage may be due either to inadequacies of the test system employed or to the fact that antibody-producing cells are "end cells" which either do not replicate at all or else lose functional ability on replication. The data presented offer no means of choosing between these alternatives. The fact that the phenomenon of splenic enlargement, which is considered to be an antigen-antibody reaction, can be serially passaged suggests that under certain conditions antibody-producing cells can retain immunological competence on replication in a foreign situation. A more definite answer will be obtained when serial passage is attempted with a wider variety of antigens and experimental recipients.

SUMMARY

When adult fowl spleen cells were inoculated intravenously into chick embryos from 11 to 20 days of incubation, the spleens of the recipient embryos became massively enlarged. The enlargement bore an inverse relationship to age with the younger recipients showing the largest spleens. Present in the spleens of only the younger embryos were large foci of mononuclear cells. These foci passed through several stages, initially showing active cellular proliferation, later peripheral reaction and cell destruction, and finally complete necrosis. This sequence of events could also be demon-

strated by the inoculation of leukocytes from the peripheral blood. When a highly inbred strain of chickens was used, transfer of spleen cells from the adult donor to embryos of the same strain resulted in very little splenic enlargement in comparison to inoculation of the same cells into noninbred embryos of the same age.

When the donor fowl had been previously immunized with heat-killed influenza virus (MEL), transfer of spleen cells to embryos resulted in the appearance of MEL antihemagglutinating antibodies in the sera of the recipients. The per cent of recipients showing antibody and the concentration of antibodies in their sera were dependent on the route of stimulation of the donor, the number of antigenic stimuli, the time interval between the last stimulus and removal of the donor spleen, and the presence or absence of antigen added *in vitro* to the cell suspension prior to inoculation. The age of the recipient embryo was also of importance with the younger (11-15 days) embryos serving as more effective recipients than the older (17-20 days) embryos. When MEL was added *in vitro* to normal, nonimmunized spleen cells prior to transfer, no antibodies were detected in the sera of recipients of any age group or genetic constitution.

Attempts at passage of antibody-forming capacity were made by removing the spleens from embryos showing high titres of MEL antibodies and inoculating the cells into further groups of embryos. Splenic enlargement and focal cellular proliferation were transferable without loss through several passages, but the ability to produce specific MEL antibodies was lost after the first passage.

Results are discussed with particular reference to their bearing on theories of antibody formation.

ACKNOWLEDGMENTS

The author in profoundly indebted to Sir Macfarlane Burnet for constant stimulation, advice, and encouragement.

The author was supported by the Royal Melbourne Hospital and served under an exchange fellowship between the Royal Melbourne Hospital and University Hospitals of Cleveland. The author wishes to express his sincere thanks to both of these institutions.

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EVENTS

YALE MEDICAL SOCIETY

December 8, 1959

BILLIONS FOR HEALTH. By William S. McNary, Executive Vice President, Michigan Hospital Service, Detroit, Michigan.

Mr. McNary commenced by giving approximate figures for the amount of money spent on medical services in the United States. During 1957, the last year for which figures were available, private expenditure totalled 15.5 billion dollars and public expenditure amounted to 5.0 billion. These figures were contrasted with corresponding 1929 totals of 2.9 and 0.77 billion dollars. At the present time more people are covered, to some extent, by various private insurance schemes than by the Blue Cross-Blue Shield plan. A review of the 1957 figures showed that private insurance paid in benefits approximately 76.1 per cent of an income of 2.175 billion dollars, and that Blue Cross-Blue Shield paid approximately 92.8 per cent of an income of 1.707 billion dollars.

One of the more pressing problems now facing the Blue Cross-Blue Shield system was described as the need to expand further its services, while recognizing that present monthly premiums were already rather high. As an example, at present in the Michigan region the premium is approximately $16 per month for a man and wife. This naturally has raised the question of how other prepayment schemes were functioning, both in terms of their acceptance by the public and of their cost. Some figures given by Mr. McNary were obtained when an industrial plant offered free choice to its employees of either the Kaiser Plan, or Blue Cross-Blue Shield. The response was overwhelmingly in favor of Blue Cross-Blue Shield, even though its rates were higher. It was noted that most prepayment plans now in effect operate under two conditions: they are opposed by the AMA and they do not allow free choice of physician. It was suggested that this latter factor may have considerable influence in the continued success of Blue Cross-Blue Shield.

Mr. McNary then ventured some predictions of what might await in the future, namely:

1) During the next generation there will be no national health insurance plan.

2) There will be a continuing expansion of voluntary plans, with the "free choice" types in the lead.

3) There will be an increase in the number of group practice units.

4) Unification will result in fewer separate Blue Cross-Blue Shield units.

5) Blue Cross-Blue Shield will offer a broader range of benefits.

6) There will be government activity in the problem of assisting the aged.

7) There will be extension of the care of the indigent by the voluntary system, with the government assuming the costs.

In his final remarks Mr. McNary said that he welcomed the emergence of new prepayment health schemes since they would provide both valuable data and competition.

S. J. F.

RESPIRATORY PHYSIOLOGY AND ITS CLINICAL APPLICATION. By John H. Knowles. Cambridge, Harvard University Press, 1959. ix, 256 pp. $5.25.

In the space of two hundred-odd pages, this book offers a thorough introduction to the whole field of lung physiology. This accomplishment, due in part to the author's admirably succinct style of composition, is also due to the relatively sparse history of the science. Pulmonary physiology is a somewhat recent discipline, contemporary concepts beginning only about 40 years ago, with the work, familiar to all medical students, of Barcroft, Haldane, Henderson, Christie, DuBois, and a few others. These pioneers failed to arouse widespread interest in their subject until two decades ago, when Cournand and his colleagues began studies which seem to have provided the catalyst for an explosive reaction resulting in a fantastic multiplication of pulmonary physiologists.

The production of sound textbooks has lagged behind this population growth, hence the addition of Dr. Knowles' monograph to the small group presently available is welcome. He has achieved a happy balance of objective review and critical discussion to provide an excellent primer for the medical student, novice in the specialty field, or general practitioner interested in broadening his medical understanding. It is lucid, readable, and accurate.

The beginner reading the book could be misled by the application of laws governing homogeneous mechanical systems to the lung, a nonhomogeneous system. This is a satisfactory expedient only when the paucity of established laws governing the lung's function is recognized. Positive assertions frequently oversimplify the clinical problems of lung disease. For example, the table differentiating primary from secondary polycythemia states that arterial oxygen saturation is "invariably" diminished in the latter, which, of course, is generally, but not "invariably," true. One might also take issue with the implication (Chapter 6) that a low ventilation-to-perfusion ratio in part of the lung could lead to an increased alveolar-arterial oxygen gradient. This is true only when compensatory hyperventilation occurs in other lung areas, since hypoventilation tends to reduce mean alveolar as well as arterial oxygen tension.

I am somewhat disappointed that bronchitis is not considered as a separate topic, for it has its own clinical and physiological consequences. Similarly, the otherwise excellent reference list lacks Stuart-Harris' and Hanley's outstanding monograph on the subject.

I disagree mildly with the author's implications, in the chapter on Aging and Senile Emphysema, that it is a matter of indifference whether changes observed in the aged are pathological or merely part of a normal process. As physicians we must attempt to cure and prevent disease regardless of the age of the patient; hence, it becomes pertinent to know whether the lungs actually change with age or whether longevity merely increases the risk of repeated noxious assaults, without which a centenarian would have the lungs of pubescence.

Many of us who teach clinical pulmonary physiology will find our task lightened immeasurably by the publication of this book.

FRANK D. GRAY, JR.

PRINCIPLES OF GENERAL PHYSIOLOGY. Vol. 1. THE PHYSICO-CHEMICAL BACKGROUND. By L. E. Bayliss. London, New York, Toronto, Longmans, Green and Co., 1959. xii, 520 pp. $11.50.

This book, with the proposed second volume, is to constitute a 5th edition of the work of the same title by the author's father, W. M. Bayliss. The last edition of that book appeared in 1924, the year of Sir William's death. Since that time his son has become known to students of the medical sciences as co-author of one of the more readable textbooks of human physiology.

The ten chapters of the present volume deal with physical chemistry, as did the early chapters of the older Bayliss, but the new treatment is considerably more advanced. The selection of topics is good and the physical chemistry is, in general, sound. However, the definition of equivalent conductivity (p. 119) is not only unusual but off by a factor of 1000. It is odd to find the electromotive force of a concentration cell without liquid junction derived from two equations for liquid junction potentials (p. 144). The equation relating osmotic pressure to the Donnan ratio (p. 273) contains two errors of sign. About a dozen other more obvious but annoying errors were noticed.

The chapters which will probably be most useful to students are the last three, on oxidation and reduction, actions of light and other radiations, and the passage of substances through membranes. These topics are more closely related to living systems than some of those discussed in the earlier chapters.

If the second volume is as good as the first, L. E. Bayliss's *Principles of General Physiology* will be a worthy successor to his father's book.

DAVID I. HITCHCOCK

THE INVERTEBRATES. VOL. V. SMALLER COELOMATE GROUPS. CHAETOGNATHA, HEMICHORDATA, POGONOPHORA, PHORONIDA, ECTOPRACTA, BRACHIOPODA, SIPUNCULIDA. THE COELOMATE BILATERIA. By Libbie Henrietta Hyman. New York, McGraw-Hill Book Company, Inc., 1959. vii, 783 pp. Illus. $13.50.

The appearance of Volume V of *The Invertebrates* by Libbie H. Hyman is especially welcome. It rounds out the general form of this monumental series by including all the smaller coelomate groups, leaving only the Mollusca, Annelida, and Arthropoda to go. The extensive treatment of these so-called "minor phyla" shores up our knowledge in areas where most zoologists are weakest. Thus fortified, we are deeply indebted to Miss Hyman.

There are several features of this book over and above its critical and comprehensive treatment of the phyla which merit special comment. Its preparation coincided with the delineation of the recently erected enterocoelous phylum, the Pogonophora, and is able to include virtually the last word said in this regard. We are thus prepared for the future accounts of pogonophores which will undoubtedly result from the extensive explorations of benthic fauna of abyssal depths. The authority of Miss Hyman as a

zoologist is such that her assignment of certain groups to phylum status will no doubt gain general acceptance and ultimately filter down into the introductory texts. Separation of Sipuniculida from Echiurida and Annelida has been long warranted. The establishment of Ectoprocta as a separate phylum from their superficially similar step-sisters the Entoprocta is entirely justifiable, thus retiring the term Bryozoa. Recognition of the Hemichordata as a phylum together with a forceful and lucid statement of their affinities with Chordata and Echinodermata is likewise convincing.

In an unusual chapter entitled Retrospect (Chap. 23) Miss Hyman undertakes to bring up to date her previous volumes by citing the outstanding works subsequent to their publication. This is necessarily incomplete and uneven in treatment, but informative and worthwhile as far as it goes. The last part of this chapter evaluates a number of concepts, some in the light of recent findings and interpretations, such as the significance of arginine and creatine phosphogens as evidence of phylogenetic relationship. Analysis of the case for and against the phylogeny of Hadzi are set forth in concise, careful, and unequivocal terms. Zoologists interested in problems of phylogeny will find this chapter and the volume in general an indispensable reference tool.

It is with regret that we note in the preface that Miss Hyman has precluded the possibility of completing more than Volumes VI and VII, Mollusca and Annelida respectively, of *The Invertebrates*. We hope that she will find it possible to reconsider this decision after finishing Volume VII and give to zoologists in completed form one of their most valuable bequests.

NORMAN A. MEINKOTH

HANDBOOK OF TOXICOLOGY. Vol. III. INSECTICIDES. Compendium by William O. Negherbon. Vol. IV. TRANQUILIZERS. Rudolph M. Grebe, Ed. Vol. V. FUNGICIDES. Dorothy S. Dittmer, Ed. Philadelphia, W. B. Saunders Company, 1959. 854 pp.; 120 pp.; 242 pp. $14.00; $4.00; $5.50.

These three handbooks represent a continuing series of publications in the biological sciences containing mainly tabular information. They are prepared under the direction of the Committee on the Handbook of Biological Data operating under the Division of Biology and Agriculture of the National Academy of Sciences, National Research Council.

The compendium on insecticides covers 164 chemical agents characterized by physical and chemical properties, and toxicities for man, plants, animals, and insects covered both in essay form and in a multitude of tables. Although the selling price of this volume is commensurate with its size and the obvious effort that went into this compilation, this reviewer feels that the page-after-page tabulation of sensitivity of every insect that has encountered an insecticide is essentially meaningless: an investigator who is interested in these results would still be forced to go to the original literature to evaluate the technique and design of these experiments. The author does give references to the original literature and in our opinion this is all that is necessary.

The volume on tranquilizers characterizes these agents under the headings, molecular formula and weight, structure, physical and chemical properties,

pharmacology, clinical, toxicity, and site of action where known. In some instances, the mode of action of the drug is also given but this is of course a futile section in view of our ignorance on this subject. References are given throughout the discussion of each drug. This handbook is satisfactory for a neophyte in this field; for the physician or for the intensive investigator, the discussion of many drugs is spotty and incomplete.

The handbook on fungicides is a condensed version of the compendium on insecticides and as such is less expensive, more readable, and to the point. It is unfortunate that suggested antidotes for each of the compounds listed are not mentioned.

JACK R. COOPER

BIOLOGICAL LABORATORY DATA. By L. J. Hale. London, Methuen and Co., Ltd., 1958. x, 132 pp. $2.75.

In this recent addition to Methuen's Monographs on Biological Subjects, L. J. Hale has compiled mathematical, physical, and chemical data often used by the research biologist. Selected biological techniques and data are also included. Whenever possible, the material is presented in tabular form. The print is bold, clear, and easy to read; the index good. The book is divided into sections on mathematical data (including tables and algebraic and geometric formulae), weights and measures, interrelationship of units, statistical data, physical and chemical data (surprisingly, this section does not include data on the physical constants of chemical compounds), saline and culture media, histological data, miscellaneous data such as symbols for correcting proof, and photographic data. References for additional information are included at the end of topics or whole sections.

The inclusion of culture media in the table of contents is somewhat misleading, since the reader will find only references to texts and articles under this topic. Although this is disappointing, it does direct a newcomer in the field to informative specialized sources. The subsection on histochemical data includes such commonly used tests as Feulgen and Schiff, but does not present any of the techniques now available for demonstrating enzyme systems. The currently active fields of immunology and chromatography are represented under miscellaneous techniques only by references.

Yet in this small versatile book one will find such diverse information as the recipe for making artificial sea water, tables for buffers in various pH ranges, and statistical equations. If it does not have what you are looking for, it does tell you where to look for it.

PHYLLIS GREENFIELD

A SYMPOSIUM ON MOLECULAR BIOLOGY. Raymond E. Zirkle, Ed. Chicago, The University of Chicago Press, 1959. viii, 348 pp. $7.50.

This book consists of a series of chapters from a number of lectures in a seminar series and a symposium held at the University of Chicago during the period November 1, 1956 to March, 1957, under the auspices of the Chicago-Frankfurt Inter-University Program. Molecular biology includes

the many and different endeavors which aim at an explanation of living phenomena in terms of molecules and their properties.

The present work by 25 outstanding scientists in molecular biology points up the tremendous upsurge of research activity on the molecular level. The book contains 20 examples of this research, all written by investigators deeply engaged in it. The chapters illustrate the diversity of the problems facing research workers and the methods for elucidating them.

Of particular interest were the chapters by Kurt Felix, principles of molecular biology; Isidore Gersh, cytochemical studies with the electron microscope; Richard L. Sinsheimer, current ideas of the structure of desoxyribonucleic acid (DNA); Arthur Kornberg, enzymatic synthesis of DNA; Alexander Rich, bearing of structural studies on relationships of DNA and RNA; Christian B. Anfinsen, protein structure and biological activity; Arthur L. Lehninger, on oxidation, phosphorylation, active transport, and mitochondria structure; Jui H. Wang, enzyme models; Julian M. Tobias and Phillip G. Nelson, structure and function in nerve, and R. E. Zirkle, structure of the mitotic spindle.

This work is a scientific *tour de force*. It is uniformly edited and impeccably published under the auspices of a scholarly publisher This book is recommended without reservation. It will enjoy a long success in the hands of scholars concerned with the dynamics of molecular biology.

JOSEPH THOMAS VELARDO

IMPLANTATION OF OVA. P. Ekstein, Ed. Memoirs of the Society for Endocrinology, No. 6. Cambridge, Cambridge University Press, 1959. vii, 97 pp. $6.00.

This work represents the proceedings of a conference held in November 1957, at the Ciba Foundation, London. It surveys the vital phase in mammalian development during which the fertilized ovum becomes implanted within the maternal bed of the endometrium. This factual and most interesting monograph is comprised of ten invited papers and a few prefatory and concluding remarks. All of the papers are by well-known European scholars working in the field of the physiology of reproduction.

The monograph records the different approaches to the general problem of the control of nidation. The morphological analysis by Professors Ekstein, Shelesnyak, and Amoroso; the histochemical analysis by Professor Boyd; the biochemical analysis performed by Dr. Lutwak-Mann all deal with the same topic, but from different angles, and with different methodology.

G. Mayer's essay on control of delayed implantation represents a new landmark for experimental endocrinology. The ingenious approach by Mayer makes it possible for the same animal to bear embryos of different stages of development, and whose developmental ages are different, although they were conceived at the same time.

Herein lies the most up-to-date treatment of implantation from endocrinological, physiological, and pharmacological aspects. Much of the information is discussed in terms of recent findings, and a great deal of data is *new* and previously unpublished. The status of this subject has evolved at a tremendous pace over the past few years, and the clarity with which newer

aspects for further exploration are defined insures future progress at an ever-accelerated tempo.

JAMES THOMAS VELARDO

REGULATION OF CELL METABOLISM. Ciba Foundation Symposium. G. E. W. Wolstenholme and Cecilia M. O'Connor, Eds. Boston, Little, Brown and Company, 1959. 387 pp. $9.50.

The book represents the written minutes of the symposium on "Regulation of Cell Metabolism" held in London on July 28-30, 1958, sponsored by the Ciba Foundation. There is no problem of greater importance to the basic understanding of biology than the study of the autoregulatory mechanisms of the cell. The participants in this conference are all leaders in the field of biochemistry and the discussions are the most authoritative possible on the selected topics.

A major portion of the book concerns control of glucose metabolism including limiting factors in glycolysis and quantitative aspects of the control of oxygen utilization. Particularly excellent is the discussion by Lehninger on oxidative phosphorylation and the chapter by Lynen on the vital importance of intracellular inorganic phosphate. The electron microphotographs presented by Siekevitz are of the highest quality and his attempt to correlate specific structures with specific reactions is an example of the imagination and forward thinking desperately needed in the study of the cell today.

Sir Hans Krebs makes clear in his introductory remarks that the conference is concerned primarily, although not exclusively, with the primitive cellular control mechanisms and no attempt is made to discuss the role of extracellular hormonal influences. The only major criticism of the book is the fact that 12 of the 17 chapters are related to the regulation of carbohydrate metabolism and only 3 are particularly concerned with nucleic acid and protein metabolism. Although the definition of feedback is extensively discussed in the final chapter, there is never any attempt made to cover thoroughly the multiple cellular feedback mechanisms already known. The work mainly involves bacterial metabolism, and such major autoregulatory mechanisms as the process of mitosis in mammalian cells are completely ignored.

This reviewer is in complete agreement with the concept that conferences with few people are the most rewarding to both the participants and to the readers of the symposia. The informal discussions at the end of each chapter are only possible with small groups, are most revealing, and provide some of the most useful information. It is hoped that this conference will be a stimulus toward many other such assemblies which over a period of time will eventually broaden the scope of this study to all aspects of cell regulation.

DONALD W. KING

CARCINOGENESIS. MECHANISMS OF ACTION. Ciba Foundation Symposium. G. E. W. Wolstenholme and Cecilia M. O'Connor, Eds. Boston, Little, Brown & Company, 1958. xii, 336 pp. $9.50.

This small volume, dedicated to Sir Ernest Kennaway (1881-1958), is a report of one of the general symposia sponsored by the Ciba Foundation and

convened under the chairmanship of Professor A. Haddow on June 24-26, 1958. It includes 21 separate reports of the papers presented and the subsequent discussions of these papers. The 29 participants at the symposium were outstanding authorities in the different aspects of carcinogenesis from 12 different countries. The general high quality of organization and reporting that has become a well-recognized feature of the Ciba Symposia is evident in this volume.

Between the first Chapter by I. Hieger on "Theories of carcinogenesis" and the "Concluding remarks" by Sir Macfarlane Burnet are sections treating specific types of carcinogens including plastic films; heavy metal with special emphasis on iron-dextran; viruses; hormones; ionizing radiation; and carcinogenic hydrocarbons and amines. The immunological aspects of cancer were discussed by Dr. H. N. Green and Dr. E. C. W. Weiler; some biochemical aspects by Dr. C. Heidelberger, Dr. G. M. Bonser, and Dr. E. Boyland; pharmacological approaches by Professor H. Druckrey and testing methods by Dr. C. Hackmann.

"The mechanism of carcinogenesis is a mirror into which we look and see ourselves" (Heidelberger, p. 164), is evident throughout the volume. The most common assumption is that cancer is a response to an agent of some type, most probably of extrinsic origin or a combination of agents given such general designation as initiators and promoters. The response is characterized by the failure of the affected cells to grow independently of the usual growth regulating mechanisms. Little unpublished data is included in most chapters, the authors drawing from the published data samples of evidence to support their hypotheses of the mechanisms of carcinogenesis. Therein lies one of the most pleasant aspects of the volume, the listing of hypotheses mostly not new, but sometimes built into new concepts and often supported by new data or interpretations, and the discussion of these hypotheses by competent scientists using other "mirrors."

The importance of studies on carcinogenesis was repeatedly emphasized. When cancer can be understood from its etiology or etiologies it is not improbable that more may be accomplished relative to its control and prevention. The organ or animal response to many of the agents grouped as carcinogens are so inadequately understood at the cellular level or subcellular level at which they presumably act that such discussion still centers around vague quantities or are considered under gross entities such as species or strains.

This small volume should be of interest and stimulating to all those interested in basic studies on experimental carcinogenesis.

W. U. GARDNER

NEUROPHARMACOLOGY. Transactions of the Fourth Conference, September 1957. By H. A. Abramson, Ed. New York, Josiah Macy, Jr. Foundation, Inc., 1959. 285 pp. $5.00.

Three of the four topics discussed at the fourth conference on Neuropharmacology of the Josiah Macy Foundation were concerned with psychotomimetic substances (LSD-25, mescaline and its congeners, and taraxein), while the fourth consisted of the description of a technique for studying self-

stimulation of an animal's brain, leading to so-called "stop and start systems."

It seems to the reviewer that almost every reader of this book, whether casual or deliberate, would be drawn primarily to the topic by Dr. Robert G. Heath entitled "Clinical studies with taraxein." This has to do with a substance separated from the serum of schizophrenic patients and claimed by Dr. Heath to produce in normal volunteers signs similar to those seen in the schizophrenic patients. It is a finding which has been rife with confusion since its first announcement, but one which, if substantiated, is so far-reaching in its implications that it demands immediate attention. Dr. Heath's presentation here has only perpetuated the confusion by the hastily formed hypotheses, and the rather weak explanation of the failure of others to reproduce these findings. Moreover, some of the confusion is traceable to the unorthodox sequence of reporting these findings earlier (the actual description of the isolation of taraxein appeared many months after the first report of its activity). It is the opinion of this reviewer that the success of this conference has been assured, if for no other reason, by the many justifiable doubts about this work which were raised, and by the avenues of future scientific attack which emerged.

Dr. Seymour Kety of the National Institute of Mental Health brought up one of the most cogent criticisms when he pointed out that once the development of abnormal behavior seemed to be set in motion by the administration of taraxein, there was unavoidably the asking of leading questions by the observer and the transmission of the observer's sense of anticipation to the subject. It is to be hoped that Dr. Heath's answer to this criticism ("If I had it to do over, I would do it the same way") does not hold promise of further prepetuation of the confusion. In addition, Dr. Heath's twice avowed concern that the "cult of controls" can retard scientific advancement (p. 142) does little to support his stand.

Dr. Heath's search for taraxein grew out of investigations and hypotheses which, in themselves, form a confused and unsubstantiated chapter in psychopharmacology: the Akerfeldt test for a vaguely defined serum oxidase; the role of ceruloplasmin and copper in mental disease; abnormal metabolites of catecholamines as endogenous psychotomimetic agents. The flaws in each of these investigations and associated hypotheses have been made clear. Thus, taraxein, the offspring of these studies, can rest on no firmer ground. In fairness to Heath, however, he has actively encouraged other groups to endeavor to repeat his work, and the answer to this problem may be forthcoming when such groups give their reports at similar conferences. There appears to be enough of a germ of truth in Heath's story to make us anxiously await the outcome.

Dr. H. A. Abramson presented an interesting report on the "Effect of respiratory poisons and anoxia on Siamese fighting fish in relation to LSD-25 reaction." Using the behavior and position of these fish in a drugged medium as an end-point, Abramson has reached the rather broad concept that LSD-25 acts in fish and in man by poisoning some parts of the cytochrome oxidase, peroxidase, catalase, or other metal-containing enzyme system, because of the similarity of its action to that of potassium cyanide.

The inference proceeding from this, according to Dr. Abramson, is that schizophrenia is a result of altered oxidative metabolism.

Again Dr. Kety produced some of the most effective comments against this idea when he indicated that over-all oxygen consumption has been shown not to be altered either in schizophrenia or in man hallucinating under the impact of LSD-25. At best, Dr. Abramson has an interesting bioassay to work with, but extrapolation of his results to delicate behavioral effects in man seems to this reviewer next to impossible.

The discussion by Dr. John C. Lilly on " 'Start' and 'stop' systems" is an extension of techniques described by Olds and Milner and co-workers and by Delgado and his group. These techniques consist of means whereby an animal can continue or stop stimulating itself in a specific region of the brain. Dr. Lilly has shown good judgment by calling these simply "Stop" and "Start" systems rather than fear and pleasure centers, and in this way has avoided the anthropomorphizing done by other workers in this field. The technique is extremely interesting and by now well established enough to offer itself to the neuropharmacologist, it would seem, for a fruitful study of the influence of pertinent neuropharmacological agents upon control situations.

Dr. Gordon A. Alles gave the final discussion on "Some of mescaline and related compounds." What seemed to be lacking here was a good neurophysiological analysis of the action of these compounds on the brain. The data presented were detailed and interesting but relatively superficial with methylene dioxy derivatives of mescaline provided fascinating reading. Dr. Fremont-Smith pointed out quite properly, of course, that it would be important to have the experiences of a group of subjects, in view of the large individual variation, especially in responsiveness of the central nervous system.

In general, this volume, like its predecessors, is of some value to individuals actively doing research in neuropharmacology and, to a lesser extent, to clinicians in fields upon which this research bears. The real drawback to the series lies in what seems to be an excessively long time lag between the presentation of the discussions and their appearance in print: in this case, almost two years.

NICHOLAS J. GIARMAN

PHYSIOLOGY OF PREMATURITY. Transactions of the Third Conference. Jonathan T. Lanman, Ed. New York, Josiah Macy, Jr. Foundation, Inc., 1959. 145 pp. $3.00.

The patterns of development of various enzyme systems during the perinatal period of life and the untoward consequences of deficiencies of certain enzyme activities in newborn, particularly prematurely born, infants are currently undergoing active investigation. This small volume contains a surprisingly comprehensive account of the recent progress in these fields.

The appearance during late fetal and neonatal life of several specific enzyme activities which allow the function of associated biochemical pathways is described with special emphasis on recent studies of the developmental aspects of tyrosine metabolism. The mechanism of glucuronidation of bili-

rubin is discussed along with the disorders, particularly jaundice and the consequences thereof, which occur in a premature infant and in members of a certain strain of rats, because both the latter groups cannot effectively conjugate bilirubin to its excretable form. A therapeutic program designed to overcome the enzymatic defect in jaundiced human infants is reviewed; unfortunately, work done since the presentation of this material has shown the procedure to be of questionable value.

This book will be of great value to those interested in the biochemistry of development both as a challenging field of scientific endeavor and as a means of understanding some fairly common clinical problems occurring during the perinatal period.

IRA K. BRANDT

THE INFLUENCE OF HORMONES ON LIPID METABOLISM IN RELATION TO ARTERIOSCLEROSIS. Annals of the New York Academy of Sciences, vol. 72, art. 14, pp. 787-1054. June 1959. Abraham Dury, Cons. Ed. $4.00.

This series of papers is the result of a conference held by the New York Academy of Sciences on April 11 and 12, 1958. The volume is striking testimony to the remarkable diversity of current research in the busy field of arteriosclerosis. The 17 papers which make up the volume include detailed studies of intermediary metabolism, of animal experimentation, and clinical investigation.

The initial papers deal with the biosynthesis, absorption, and transport of lipids. There follows a series of papers on the role of the pituitary, thyroid, adrenal cortex, adrenal medulla, parathyroid, sex hormones, and pancreas in cardiovascular disease. A final group of papers is concerned with the endocrines, ground substance, and tissue permeability. Several authors commented on the problem of the similarity, or lack of it, between the type of medial necrosis of the artery wall caused by such agents as epinephrine or parathyroid hormone, and the fatty sub-intimal lesions usually characteristic of human atherosclerosis and of dietary-induced animal atherosclerosis. In another paper the frequently alleged but unproved association between hypothyroidism and atherosclerosis is exposed as an unfounded myth.

In a sense many of the presentations are too specialized for a collection of such general interest, yet the helpful discussions at the end of each group of papers serve to bring each subject into the focus of the general problem. This volume is not necessarily a complete coverage of the subject set forth in the title, but is rather an interesting sampling of work going on in the field, and a rich source of provocative new ideas.

MARGARET J. ALBRINK

YALE UNIVERSITY SCHOOL OF MEDICINE

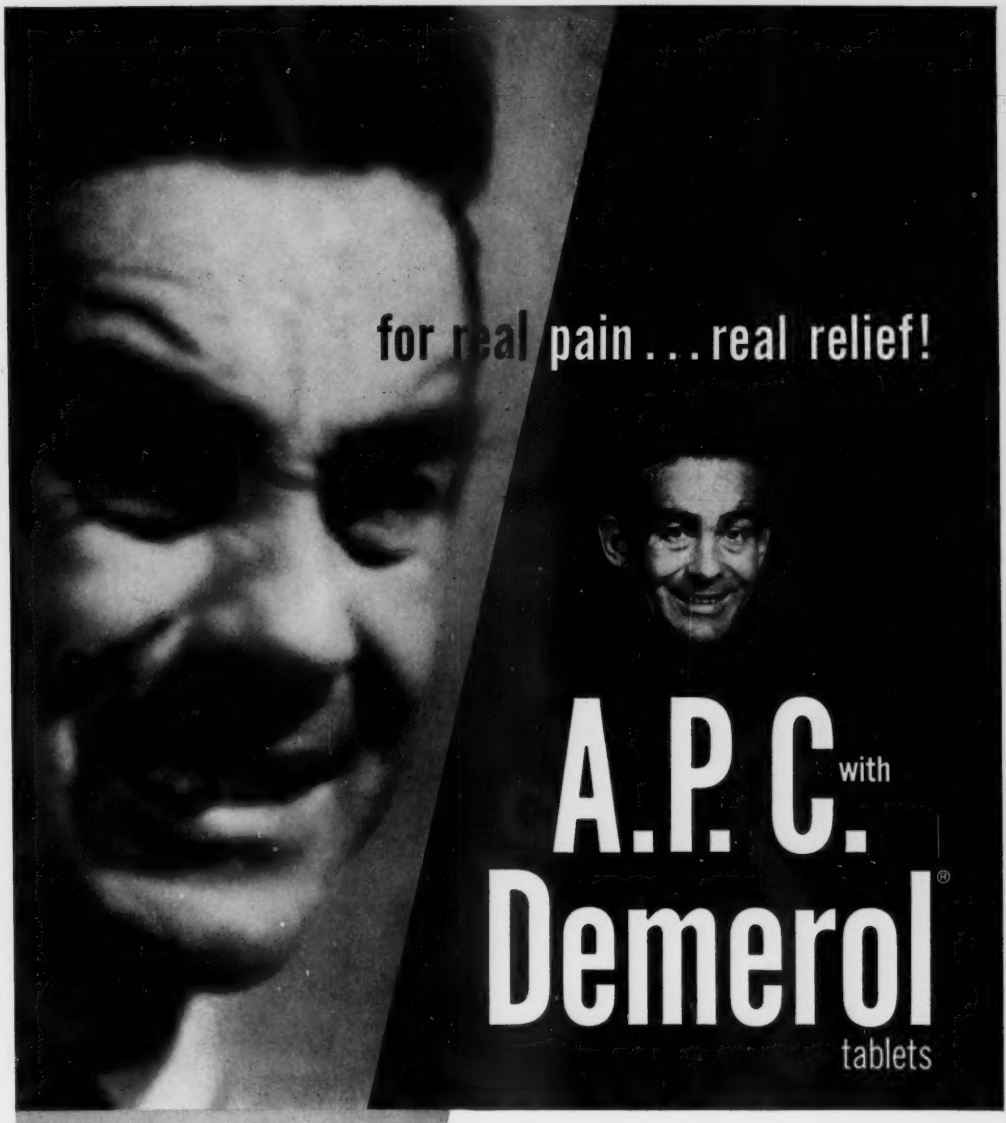
TO CELEBRATE SESQUICENTENNIAL

The Yale School of Medicine will celebrate a century and a half of existence on October 28 and 29 of 1960. The occasion will be marked by meetings, exhibitions, and addresses suitable to the occasion. Among a notable group of guest speakers will be Sir Howard Florey of Oxford, England. Complete details of the program will be announced later.

It was in October 1810 that the Connecticut General Assembly granted a charter to Yale College for the establishment of the Medical Institution of Yale College; the fifth medical school in the United States thus came into being. Unlike its predecessors, the medical school was founded through impetus coming chiefly from within the College and not from a group of outside physicians.

The first medical faculty at Yale was a notable one, containing Eneas Munson, foremost authority on materia medica, Nathan Smith and Benjamin Silliman, still counted among Yale's greatest, Eli Ives and Jonathan Knight, leaders in medicine who were each to become President of the American Medical Association. From the start, the Connecticut Medical Society was a partner in the enterprise and worked in close cooperation during the first half century of the School's existence.

Other events associated with the sesquicentennial celebration will take place during the academic year 1960-61. These include a scientific meeting to be held in conjunction with the dedication of a new Medical School auditorium.



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